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ORIGINAL ARTICLES

INCONCLUSIONS OF STUDIES, MOSTLY OF PREMATURE INFANTS

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ONE of the duties of the President of the Society for Pediatric Research is the selection of papers for the annual meeting. In order to give as many people as possible a chance to present their data before the Society, only 10 minutes are allotted for each speaker. This tends to put a premium on black and white; the exploration of shades of grey is relegated to the boardwalk, hotel lobbies, rooms and bars. Since this is my last opportunity to appear on the Society's program as an active member, I should like to review not our summaries and conclusions, but rather, some of the problems we did not settle, an "outline of ignorance,"[1] as it were.

Our studies of prematurely born infants began in conjunction with Dr. S. Z. Levine at the New York Hospital in 1932, with a survey of the literature on the fetal endocrine system and on the physiology of premature infants. This was stimulated by the then Director of Laboratories at Montefiore Hospital, Dr. David Marine, who had called to our attention the postnatal involution of the adrenal cortex of both premature and mature infants. He had related this to the postnatal rise in basal metabolism of full term infants,[2] a rise subsequently found in premature infants as well[3] but one which we could not justifiably relate to any single postnatal factor. The opportunity to review this literature before starting to collect data served as an introduction to the complexity of neonatal adjustments, and warned us against becoming what Whitehead has termed "provincial in time."[4]

In figure 1 is presented, for nostalgic reasons, the calorimeter for premature infants, modified in stages from the Russell Sage calorimeter for adults and the children's and infants' calorimeters used by Levine and Wilson.[5,6] These were the days, when determining that an alcohol lamp consumed two volumes of oxygen for every three of carbon dioxide produced, i.e., R.Q. of 0.667, when the report of Miss Margaret Kelly or her assistant, the late Miss Helen Schnetzer, that an infant had retained all of the formula

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ingested during the previous 24 hours and that there had been no losses of urine and feces, constituted a sure defense against external irritants. I mention these to cite their abiding value for peace of mind in a world which seems to vary only in the degrees of its

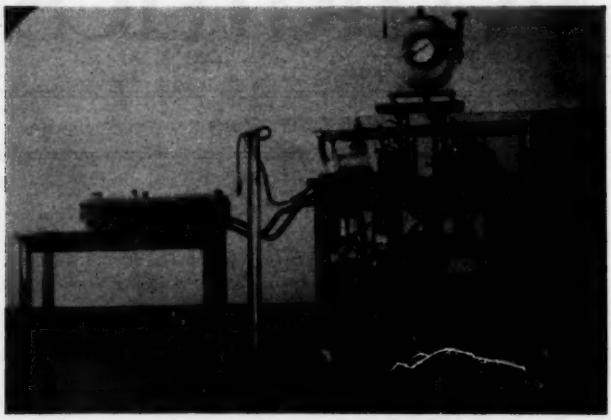


FIG. 1. Open circuit apparatus used in measuring respiratory metabolism of premature infants (From Gordon, H. H., and others, Respiratory metabolism in infancy and childhood, Am. J. Dis. Child. 59:1185, 1940.)

madness, one in which the way of much flesh has led me to a position in which I have to accept satisfaction from such substitute rationalizations as raising funds for research and concepts like "symbolic representation of unity of purpose" in a department.[7]

The first data we wish to show (see chart 1) compare the basal metabolism of prematurely born with that of full term infants (charts 2 and 3).[8] The results indicate that

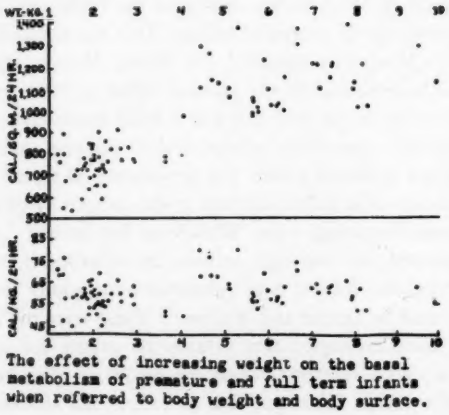

WT-KG.
CAL./SQ. M./24 HR.
CAL./KG./24 HR.
The effect of increasing weight on the basal metabolism of premature and full term infants when referred to body weight and body surface.

CHART 1

(From Gordon, H. H., and others, Respiratory metabolism in infancy and childhood, Am. J. Dis. Child. 52:810, 1936.)

prematurely born infants have approximately the same caloric expenditure as full term infants when referred to body weight, but much less when referred to body surface. We still cannot go beyond this statement of fact in trying to estimate whether the rate of oxidation in the cells of premature infants differs from that of full term infants.

One of the troublesome factors is indicated in table 1. It is seen that a premature infant

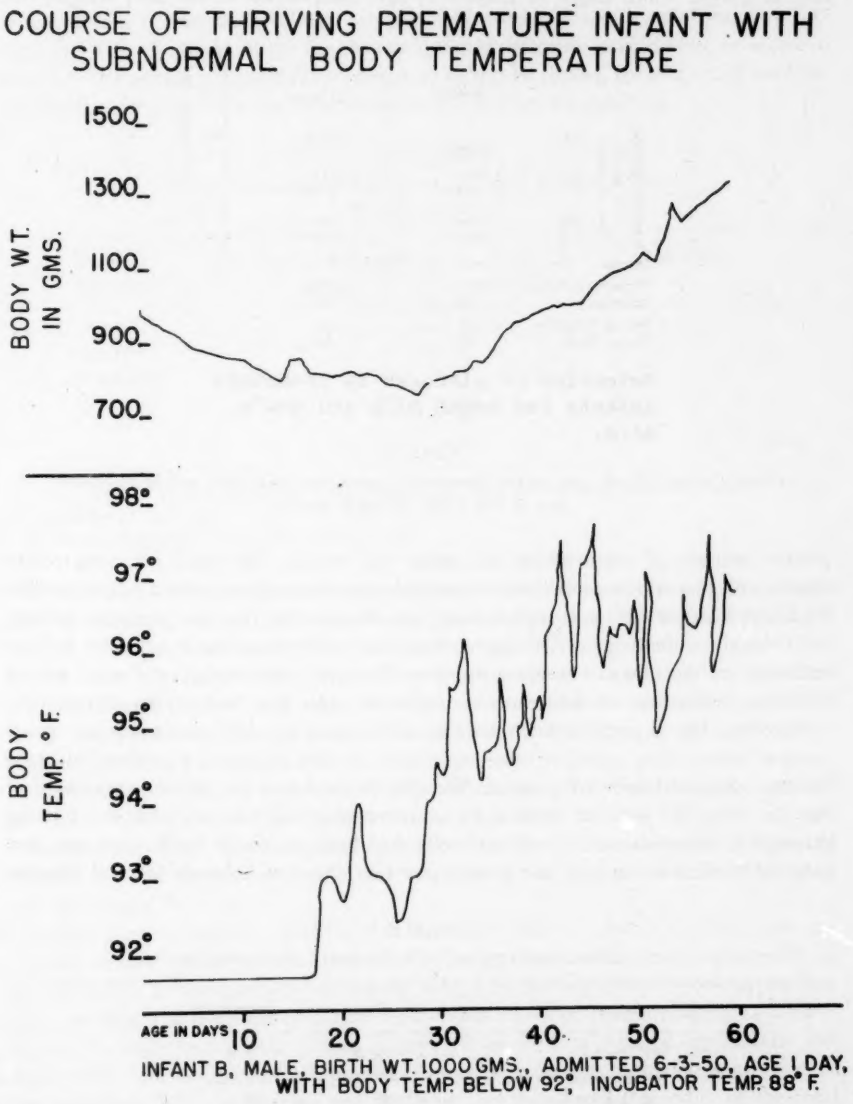
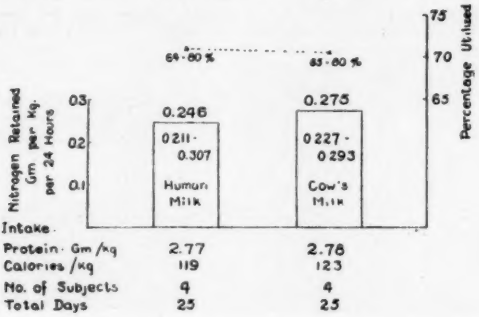


CHART 2

of 1.5 kg. who produces 60 cal./kg./24 hr. has a basal metabolic rate referred to surface area which is 16% less than that of a full term infant of 3 kg. who produces the same 60 cal./kg. and this because the relative surface varies inversely with the mass. These observations led to a consideration of factors[8–10] which may affect total oxygen consumption: size of the individual; previous diet; environmental temperature; rate of and therefore heat of growth which might be affected by age; composition of the body weight, i.e.,



Retention of nitrogen by premature infants fed human milk and cow's milk.

CHART 3

(From Gordon, H. H., and others, Respiratory metabolism in infancy and in childhood. Am. J. Dis. Child. **54**:1030, 1937.)

relative amounts of subcutaneous fat, muscle and viscera. We could not compare our infants with marasmic infants[11] who resembled premature infants in their lack of insulating fatty tissue, but who were convalescing from illness, older than our premature infants, and unhappy in the bargain. The limitations of our ability to define these factors led to a realization of the limits of studying the over-all oxygen consumption, and to an interest in studying indications of differences in metabolism other than total oxygen consumption.

Since heat loss is partially determined by surface area, low heat production per square meter of surface does constitute some explanation of the tendency of premature infants to develop subnormal body temperature. We still do not know the clinical significance of this. In 1939, Dr. Blackfan showed me a premature infant who was pink and thriving although his temperature in previous weeks had been as low as 89°F., and was then only 94°F. Since we opened our premature infant center at Colorado General Hospital

TABLE 1

COMPARISON OF CAL./SQ. M. OF SMALL AND LARGE INFANT

	Term	Premature
Wt. (kg.)	3.0	1.5
Surface area, sq. m.	.210	.125
Cal./kg./24 hr.	60	60
Cal./sq. m./24 hr.	857	720
Deviation		−16%

in 1947, we have housed our premature babies in incubators in which the environmental temperature is fixed at a reading between 80°F. and 90°F., varying with the size of the infant, but not with the readings of the baby's axillary temperature.

Chart 2 shows the course of one infant whose axillary temperature was below 33.3°C., the lowest reading on our clinical thermometers for almost three weeks. Many of our small infants have temperature curves like this one. It seems fair to conclude that low body temperature is not inconsistent with survival of premature infants, a point made by Eckstein in 1926.[12] Recently, Miller has suggested that hypothermia may increase resistance to anoxia.[13] We are not suggesting that premature infants be chilled, but that one desist from inordinate attempts to raise the body temperature if it is low on admission.

TABLE 2

UREA CLEARANCE OF PREMATURE AND FULL TERM INFANTS*
(cc./sq. m./min.)

Age Days	Premature		Full Term	
	No.	Mean	No.	Mean
Under 30	21	13.7	6	17.3
30 and over	14	17.6	6	24.6
Total	35	15.3† P.E. ±0.47	12	21.0† ±1.08

* From Gordon, H. H., and others, Urea clearance of young premature and full term infants, J. Clin. Investigation 21: 499, 1942.

† Difference between means is 5.7 ± 1.18.

In the course of our calorimeter observations, examination of the urinary nitrogen showed a lower excretion of nitrogen in the urine of premature infants fed human milk than of those fed cows' milk.[3] This fitted with accepted views concerning a higher "biological value" of human milk protein. When this was checked in observations of infants fed human milk or cows' milk mixtures of the same total calories and protein, no differences in nitrogen retention were found.[14] (See chart 3.) These data are presented today because of two incidental observations.

It was noted that edema developed in some infants when they were changed from diets of human milk to diets of cows' milk containing equivalent amounts of protein, fat, carbohydrate and water. This suggested a lag in excretion of the additional sodium and chloride ingested in the cows' milk, and led to studies of urea clearance with Harrison and McNamara.[15]

A significant deviation in renal function was found (table 2) which has been more particularly defined by the work of others.[16–19] The problem of the precise relationship of tubular defects in young infants to unstable water and electrolyte balance remains unclear. Our own efforts to study the effects of limited fluid intake on concentrating ability led to equivocal results because our infants became ill before they attained significantly low urine flows; and we began to think about intracellular defects in maintenance of ionic concentrations. With McNamara and Benjamin, we then tested the ability of the renal tubules to form ammonia and conserve fixed base in response to NH_4CL ingestion.[20] The plan of study was essentially that of Gamble, Blackfan and Hamilton.[21] The three pre-

mature infants studied excreted respectable amounts of excess chloride—a result not to be expected from the work of Darrow,[22] but fortunate for the purposes of our study.

Two of the three premature infants, S.L. and A.H., showed a defect in ability to make NH_3 and conserve Na when compared with the full term infants. We see, however, that although the two smallest infants become sick, only one of them, S.L., showed the defect in ability to make ammonia, and they both gained weight while their subcutaneous tissues became dehydrated and their fontanelles depressed. (See table 3.) Furthermore, there was no correlation between the plasma levels of CO_2 or chloride and the existence of illness. Here again, we find a suggestion of some deficiency in intracellular defenses, points discussed by Branning and McBryde, and by Reardon, Graham, Wilson and their coworkers.[23–25]

A second incidental observation made during our studies of nitrogen metabolism was

TABLE 3

RELATION OF EXCRETION OF EXCESS AMMONIA AND NA TO EXCESS CHLORIDE DURING ADMINISTRATION OF NH_4Cl*

Infant	Wt. (kg.)	Condition	Excess NH_3 % Cl	Excess Na % Cl	Wt. Change
S.L.	2.0	sick†	21	52	+40
M.R.	2.3	sick†	64	15	+30
A.H.	2.8	well	36	40	+40
D.S.	3.7	well	114	−24	+260
D.F.	4.6	well	62	13	+170
D.H.	5.8	well	51	19	+60

* From Gordon, H. H., and others, Response of young infants to ingestion of ammonium chloride, PEDIATRICS 2: 290, 1948.

† Fontanelle depressed; skin dehydrated; listlessness; refusal to nurse.

TABLE 4*

EFFECT OF VARYING AMOUNT OF DIETARY FAT ON EXCRETION OF FAT

Days	Dietary Fat gm./kg.	Fecal Fat		Wt. Gain gm./kg.
		gm./kg.	% Dietary Calories	
Infant P.A.			(a)	
10	1.8	1.0	9	14
8	1.9	0.8	7	15
7	4.7	1.9	16	7
9	2.1	0.7	5	16
Infant H.A.			(b)	
11	2.2	1.2	10	13
8	2.1	1.1	9	15
7	4.1	3.3	27	5
9	2.1	0.7	5	14

(a) 108–114 cal./kg. in diet
(b) 111–118 cal./kg. in diet

* From Gordon, H. H., and others, Metabolic basis for individualized feeding of infants, premature and full-term, J. Pediat. 25: 464, 1944.

the finding that some premature infants absorbed fat poorly.[26] This confirmed the findings of Rubner and Langstein, Muhl and Holt, Jr., and his co-workers.[27-29]

The significance of this deviation for weight gain is shown in table 4. The two surviving members of a set of triplets showed much better gains on isocaloric feedings of low fat than on mixtures of customary fat content.[30] We considered this as direct confirmation of

TABLE 5

EFFECTIVENESS OF VARIOUS AGENTS IN REDUCING TYROSYLURIA

Animal	Deficiency	Dietary Supplements			
Guinea pig[38-41]	Scurvy	Ascorbic acid		+	
		Liver extract		+	−
		PGA		+	
Monkey[42]	Ascorbic acid and PGA (Megaloblastic anemia)	Ascorbic acid		+	
		PGA			−
Albino rat[43]	Tryptophane	Tryptophane		+	
		Cystine			−
	Lysine	Lysine		+	
		Cystine			−
	Methionine and cystine	Cystine		+	−
		Cysteine		+	−
		Methionine		+	
		Ascorbic acid	?	+	−
Humans	Pernicious anemia[44,45]	Liver extract		+	
		Desiccated hog stomach		+	
		B_{12}		+	
		Ascorbic acid			−
	Scurvy[46-48]	Ascorbic acid		+	
		PGA		+	−
		B_{12}			−
	Full term infants, high protein diet plus tyrosine without ascorbic acid[49,50]	Ascorbic acid		+	
		PGA		+	2/2

Powers' experience that premature infants seemed to do better on low fat feedings.[31] These implications were confirmed in a much larger clinical study [32] but we must point out that the data have yielded no information concerning the pathogenesis of this deviation, which remains as obscure as that in celiac disease.

We go back now to the urine collected in the original calorimeter specimens. Because Paffrath and Ohm[33] had reported absent or diminished creatinuria in premature infants, and because Levine and Marples were studying creatinuria in full term infants, the calorimeter specimens were examined for creatine. The existence of diminished creatinuria was confirmed.[34] This led to many determinations of urinary creatine,[35] but comparisons under stress with full term infants were never made, and studies aimed at deciding whether the defect noted is one of deficient diet, retarded excretion or faulty synthesis are now being conducted at the University of Colorado.

In the studies of creatinuria, Marples found a chromogenic substance which interfered with the Jaffe reaction, and she came within a half a molecule of water of identifying it as p-OH phenylpyruvic acid. Since thiamine was important in the metabolism of pyruvic acid and since Closs and Fölling[36] had shown that phenylpyruvic acid was excreted by thiamine deficient rats, thiamine as well as other then known factors of the B complex were administered without significant effect. It was then decided to try ascorbic acid, another water-soluble vitamin. The two subjects shown in table 4 on relation of weight gain to fat intake were the first infants in our metabolic studies who had received no ascorbic acid, and they were the first two infants who continued to excrete "tyrosyl." The administration of ascorbic acid led to prompt abolition of tyrosyluria.[37] This effect of ascorbic acid was established independently in scorbutic guinea pigs by Sealock and Silberstein at about the same time.[38]

TABLE 6

EFFECTIVENESS OF VARIOUS AGENTS IN REDUCING TYROSYLURIA OF PREMATURE INFANTS ON HIGH PROTEIN DIETS WITHOUT ASCORBIC ACID

Uniformly Effective	Sometimes Effective[51]	Not Effective[51]
Ascorbic acid[49–51]	PGA 5/20	Vitamin A
ACTH[52]	Folinic acid 1/7	Vitamin D
	Liver extract 2/10	Cortisone 0/3*
	B_{12} 2/7	α Tocopherol 0/2
	BAL 1/7	

* Levine and his co-workers have reported cortisone effective 3 times in 8 trials (American Pediatric Society, May 4, 1951).

The exact nature of the enzymatic mechanism or mechanisms responsible for the eradication of the tyrosyluria remains obscure. In tables 5 and 6, we have listed some of the circumstances under which it occurs, and some of the effective agents.

The nature of the conditioning factor or factors responsible for the varying effect of some of the substances given, or the possible existence of alternative metabolic pathways has not been determined. Because of the recent work of Nicol and Welch,[53] we had hoped that folinic acid would prove to be the bridge between the ascorbic acid and folic acid effects, but we have had only one successful trial in seven attempts. The use of BAL has been effective only once in seven trials and the antioxidant, alpha tocopherol, has been ineffective. We have a sense of much darkness concerning the mechanism or mechanisms by which the phenol ring is broken open, almost as much as about the origin of fever in infection.

Finally, we wish to mention some work on malaria, which with Drs. Stuart Lippincott and Alex Marble, we had begun in 1943 at the Harmon General Hospital, Longview, Texas. The large number of recurrences of South Pacific vivax malaria in American soldiers had led to the suggestion that prompt treatment was interfering with development of immunity. Dr. Francis Dieuaide, then a member of the staff of the Surgeon General of the U. S. Army, made it possible for us to study this problem by: (1) arranging for the establishment of a U.S.P.H.S. insectory at Harmon General Hospital; (2) having the hospital designated as a center for the treatment of neurosyphilitic soldiers; (3) obtaining permission for us to use naturally induced malaria for treatment.

The results which are presented in table 7 indicate that delay in treatment, until the

soldiers had had 8 to 12 paroxysms and a total of 40 hours of fever above 40.0°C., did not increase the resistance to an initial relapse, since the rates of 68% and 74% were approximately the same after either delayed or prompt treatment.[54]

The problem of immunity to malaria is not simple.[55-60] In charts 4 and 5 we present an experience with D.W., who came to us for treatment of neurosyphilis. He was a former Arkansas farmer who, according to his history, had presumably had malaria in civilian life, i.e., febrile illnesses which had responded to quinine, and who had never been outside the continental United States. Mosquitoes carrying the Chesson strain[61] of South Pacific vivax malaria were permitted to feed on him. After proper incubation period, he developed fever and parasitemia; apparently his presumed previous experience with an American strain of malaria did not prevent his infection with the Chesson South Pacific strain. In spite of the fact that smears of his peripheral blood later showed parasites at densities

TABLE 7

RATES OF RELAPSE FOLLOWING QUINACRINE TREATMENT OF VIVAX MALARIA OF SOUTH OR SOUTHWEST PACIFIC ORIGIN*

	Delayed Treatment of First Attack of Naturally Induced Malaria	Prompt Treatment of Relapse of Naturally Acquired Malaria
No. of cases	50	124
No. of relapses	34 (a)	92 (b)
% relapse	68	74

(a) Average period of observation of nonrelapsers 103.1 ± 5.3 days.
(b) Average period of observation of nonrelapsers 143.2 ± 7.4 days

* From Gordon, H. H., and others, Relapse following delayed treatment of naturally induced vivax malaria of Pacific origin, Science 103: 391, 1946.

with which previously he had had fever, there was virtually no fever from the 8th to the 19th day. This change in pyrogenic threshold, i.e., the density of parasites which produces a given fever, is not an uncommon finding and suggests a changing "clinical tolerance" as the infection proceeds.[56] At the end of 41 days, he was fed up with confinement to the ward and was treated with quinacrine.

Nine weeks later he relapsed, again with parasitemia and without fever. Thus, D.W. had immunity to malaria as measured by his ability to keep parasites from multiplying at a rapid rate in his blood stream and by his ability to tolerate their presence in his blood without much fever; he did not have immunity as measured by his susceptibility to infection, nor by his tendency to relapse, i.e., exoerythrocytic parasites persisted in his body.[62] Both extracellular and intracellular factors are involved here.

These data are presented partly as encouragement that some of you who are called to the armed services may have an opportunity to continue with research or equally satisfying intellectual and emotional experiences.

SUMMARY

We do not know whether or how the rate of oxygen consumption by the cells of premature infants differs from that of full term infants. We do not know the clinical significance of subnormal body temperatures in premature infants. We do not know how much immature renal function and how much handicaps in intracellular defenses contribute to

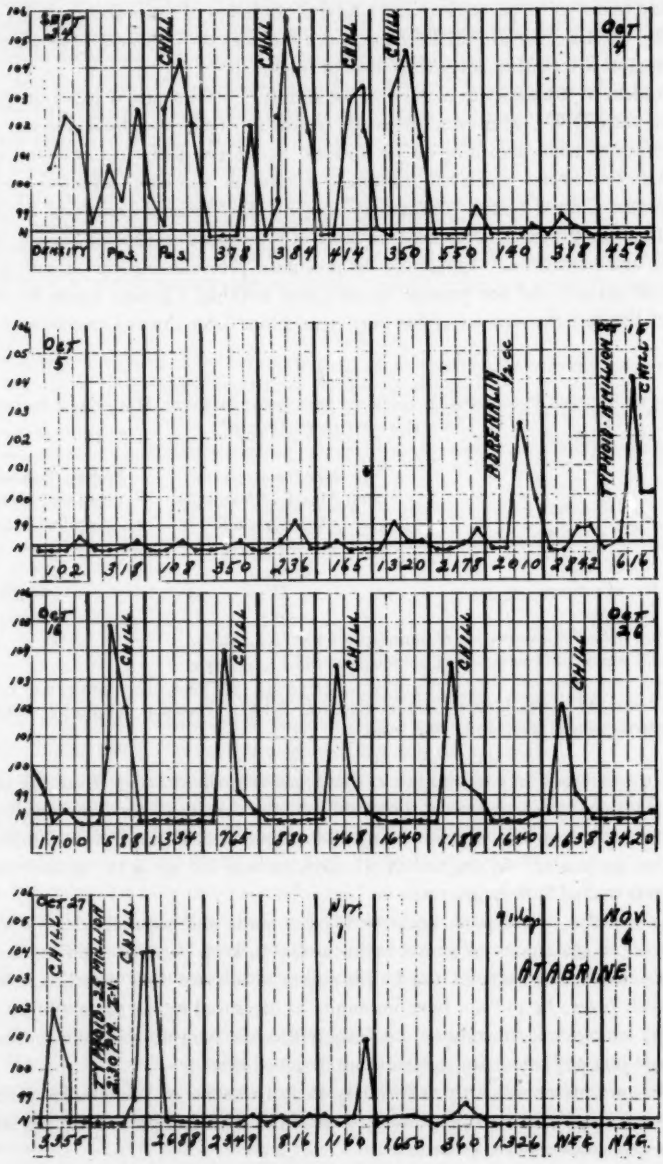


CHART 4

COURSE OF UNTREATED MALARIA NATURALLY INDUCED IN PATIENT D. W. WITH PREVIOUS HISTORY OF MALARIA

Density of parasitization of blood is indicated by "Pos." for positive thick smears only, or number, which represents parasites/cmm. of blood in daily morning count.

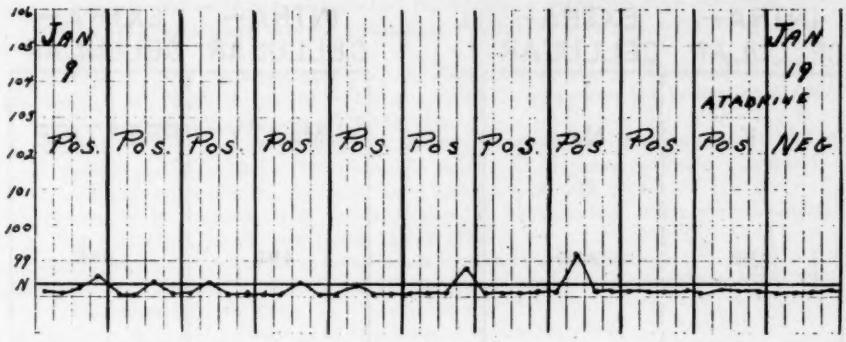


CHART 5

MALARIA RELAPSE IN PATIENT D. W. WITH PARASITEMIA BUT NO FEVER BEGINNING 9 WEEKS AFTER CESSATION OF PREVIOUS ATTACK

(Only thick smear of blood positive for parasites.)

the tendency of premature infants to develop disorders of water and acid-base balance. We do not know the nature of the deviation in ability of premature infants to absorb fat. We do not know how ascorbic acid and other dietary factors promote breaking open of the phenol ring of tyrosine or phenylalanine. We do not know what constitutes "immunity" to malaria.

This is a doleful summary; it is a consolation to note the epigram of Rabbi Tarfon, written almost 1,900 years ago: "It is not for thee to complete the work, but neither art thou free to desist from it."

CONCLUSION

Having had the good fortune to profit mightily from good preceptors and from good facilities, we cannot help feeling humble before the work that remains to be done. In chart 6, we have a simplified presentation of some important extracellular and intracellular constituents. No one will deny that a certain intake of Na and Cl is necessary for maintenance of health. Work by Butler, Darrow, Gamble, Guest and others has indicated, however, that the membrane separating the two compartments is not as selectively impermeable as had been visualized. Excessive intake or defective excretion due to disease or immaturity may lead not only to swelling of the extracellular compartment and distasteful appearance, but also to intracellular losses.

Furthermore, there is no replacement for the protein constituent. Graham Lusk once told a class of second year medical students at Cornell that the pleasure of original work came from doing the work, not from doing it ahead of someone else. An example of this pleasure is indicated in the following published anecdote by Dr. Park: "The discovery of acidosis in connection with this disorder of infants (diarrhea) was made simultaneously by Oscar Schloss of New York City who, learning of Howland's and Marriott's results, very gallantly withheld his own publication until theirs had appeared."[63]

The primary concern should thus be satisfaction in one's daily work, posing questions and finding answers which pose other questions. One is thus relieved of considerations of priority, so-called practical importance, and secondary gains. In short, in a competitive form of society which has been described by Maurice Samuel as an organized provocation

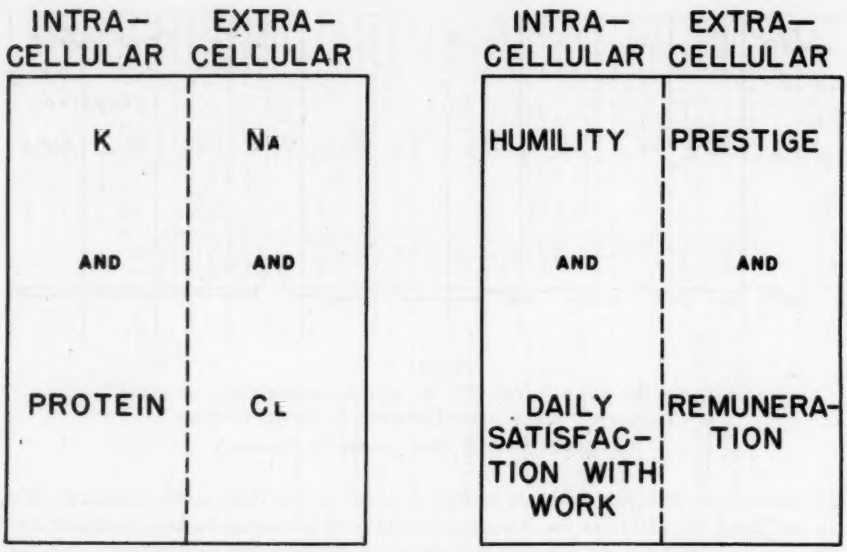


CHART 6

SOME IMPORTANT INTRACELLULAR AND EXTRACELLULAR CONSTITUENTS

of envy, one may avoid a "downward path to wisdom"[64] and become, to a significant degree, intracellularly independent.

At the 1938 dinner of this Society, Dr. Gamble stated that one purpose of our meetings was to provide young investigators with a "sympathetic but critical audience of their contemporaries." Since we are about to begin the presentations of scientific papers, I should like to leave with you a truncated version of Micah's injunction: "Love mercy, do justly, walk humbly."

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INHIBITION OF GROWTH AND OTHER EFFECTS OF ACTH IN PREMATURE INFANTS

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A REVIEW has been presented[1] of the ophthalmologic aspects of the cases of retrolental fibroplasia observed in the course of one year's admissions to the premature nurseries of Babies Hospital and Lincoln Hospital in the City of New York. Nineteen of these infants were treated with adrenocorticotrophic hormone (ACTH). The indications for treatment and the course of the ocular disease in relation to treatment are also discussed in that report. The present paper is concerned with the systemic effects of ACTH administration in this treated group of premature infants.

Fifteen of the treated cases of retrolental fibroplasia developed in the population of the premature nursery of Babies Hospital and these patients received hormonal therapy during the course of their hospital stay. Four patients were transferred from the premature nursery of Lincoln Hospital to the general infant ward of Babies Hospital for treatment with ACTH.

I. CLINICAL EFFECTS OF TREATMENT WITH ACTH

The age of the infants under hormone treatment ranged from 15 to 84 days. The hormone was given in courses of 9 to 27 days with dosage varying from 1.7 to 20 mg./kg./day. Five infants received second courses of ACTH.

Except for the one infant who received the smallest daily dose of ACTH, hyperirritability was noted uniformly during the course of ACTH administration. These infants squirmed, kicked, rooted and cried excessively during therapy, in contrast to their relatively placid pre- and post-treatment behavior. This irritability was often interpreted as evidence of hunger and several infants took and retained large volumes of formula. One infant received as many as 225 cal./kg./day. In no instance was it possible to pacify the irritable infant by offering increased amounts of formula. One attempt at sedation with phenobarbital failed to quiet a particularly irritable infant.

Immediately after the injection of ACTH many of the infants became pale. This pallor lasted for several hours and, although the general appearance of the babies was occasionally alarming, in none of them was it more than a transient phenomenon. Pallor appeared more frequently after the larger individual doses (6.25 to 10 mg.) but did not occur consistently with the same dose or lot number of ACTH. Attempts to obtain blood pressure readings before and after each dose of ACTH were not successful.

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During the latter part of treatment periods tachycardia, pitting edema, papular skin eruption, regurgitation and Cushing facies (Fig. 1) were noted. These manifestations were not constant and were not sufficiently marked to cause alarm. The dose of ACTH was never reduced or stopped because of these findings.

Prompt and sustained eosinopenia occurred regularly with all doses of ACTH employed. Serum sodium and potassium levels were not altered during the course of therapy in four infants so studied. Transient hyperglycemia and glycosuria were noted irregularly during the course of treatment. Electrocardiograms taken during ACTH administration revealed occasional sinus tachycardia; no T-wave or QRS complex alterations appeared.

Diarrhea occurred during the course of therapy in two infants. One 2800 gm. infant was receiving ACTH 25 mg./day and a 4400 gm. infant was receiving 40 mg./day when

FIG. 1. Cushing facies in premature infant. Identical twins are shown at age of 103 days. (Left) L. W. after course of ACTH (11 mg./kg./day for 20 days). No pigmentation or hirsutism was noted. (Right) V. W., who received no ACTH.

diarrhea occurred. In both cases intercurrent infection was presumed to have been the cause of diarrhea.

One infant developed a severe hand infection, caused by Staph. aureus hemolyticus, that required incision and drainage during the course of the therapy. The dose of ACTH (approximately 11 mg./kg./day) was continued, bacitracin applied locally, and penicillin and chloramphenicol given systemically. The hand healed quickly without complications. Fever was not present at any stage of this infection.

One patient developed a cough and rhinorrhea on the seventh day of hormone therapy. The infant did not appear acutely ill and physical examination of the chest showed no signs of consolidation. Neither fever nor leukocytosis was present. Roentgenograms of the chest, taken on the eleventh day of ACTH therapy, revealed extensive bronchopneumonia. Antibacterial therapy was instituted and the lung changes cleared promptly.

II. Influence of ACTH on the Urinary Output of Formaldehydogenic Steroids*

The 24 hour urinary output of formaldehydogenic steroids of untreated premature infants increased directly with increased body weight (chart 1). Following the administration of ACTH the 24 hour output of "corticosteroids" increased rapidly and remained markedly elevated during the course of therapy. One infant received tapering doses of ACTH from 11 mg./kg./day to 1.7 mg./kg./day. The urinary output of "corticosteroids" rose sharply to a level more than six times the pretreatment value, and fell with the re-

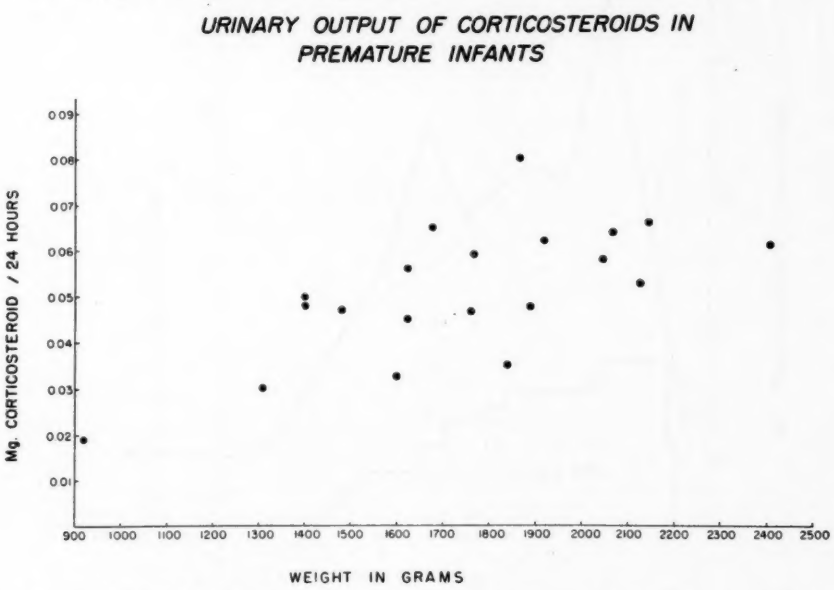

Chart 1. Twenty-four hour excretion of formaldehydogenic steroids in urine of untreated premature infants. Increasing output with increased body weight.

duction of the dose to reach the original value within one day after cessation of treatment (chart 2). The 24 hour "corticosteroid" output, under the influence of comparable doses of ACTH/kg. body weight, varied considerably in different infants but with all except the lowest doses of ACTH the output was significantly higher than in untreated subjects (chart 3).

A four month old, 4300 gm. premature infant with late cicatricial lesions of retrolental fibroplasia was admitted to Babies Hospital at a date after completion of the one year study considered in the present report. Increasing doses of ACTH, beginning with 9 mg./kg./day and ending with 19 mg./kg./day, were administered for a 23 day period.

* All determinations of formaldehydogenic steroids were performed by Dr. G. Ehrlich in the laboratories of the Institute of Ophthalmology according to the chemical method of Daughaday et al.,[2] which measures the amount of formaldehyde liberated following oxidation with periodic acid. The values obtained are calculated with reference to a "cortin unit" defined by Daughaday.

Peak excretions of 0.90 and 0.98 mg. of "corticosteroid"/24 hours were noted with a dose of 14 mg. ACTH/kg./day. When the dose was increased to 19 mg./kg./day, the 24 hour urinary excretion of "corticosteroid" fell to 0.70 and 0.71 mg.

III. Influence of ACTH on Growth of Premature Infants

1. Weight Gain.—Daily weights were obtained during the course of ACTH administra-

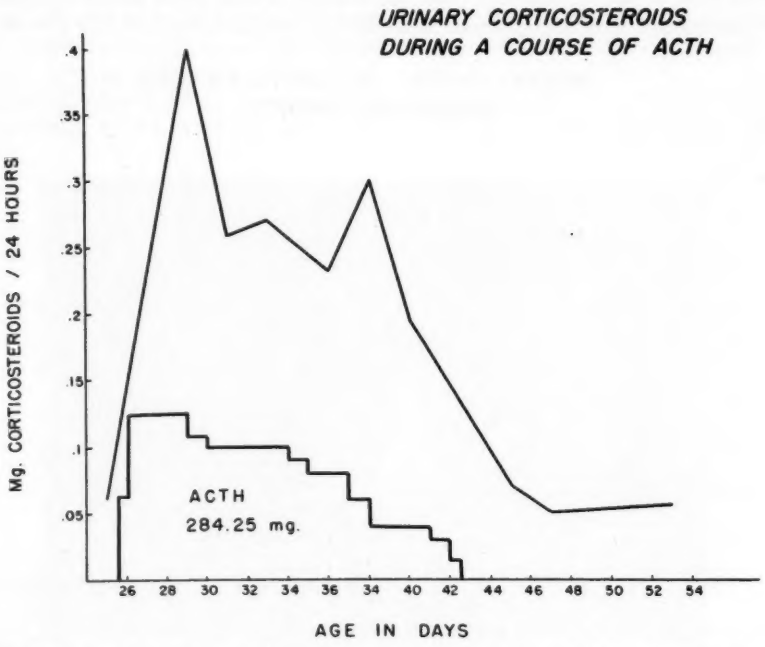

Chart 2. Urinary output of formaldehydogenic steroids under influence of tapering doses of ACTH (from 11 to 1.7 mg./kg./day). Birth weight of this infant was 1775 gm. Therapy was begun at age of 25 days, at which time weight of infant was 2080 gm.

tion. The average daily weight gains, calculated for comparable periods before, during and after ACTH therapy, are recorded in table 1.

Pretreatment weight gains were slowed immediately after the institution of treatment in all but the initial course of ACTH given the youngest infant. H., aged 15 days at the time of starting treatment, received approximately ACTH 12 mg./kg./day for 15 days. Before the start of therapy the normal postnatal weight gain had just begun. While the patient received ACTH the average daily gain was 26.4 gm./day, a rate which can be regarded as approximately normal for an infant of this birth weight.[3] The 24 hour urinary "corticosteroid" output on the fourteenth day of this course of ACTH was found to be 0.52 mg. as compared with a pretreatment excretion of 0.035 mg./24 hours. Following cessation of ACTH, rapid increase in weight occurred and continued for the following 7 days at an average rate of 52.8 gm./day, despite re-institution of ACTH 36 hours after completion of the initial course. The second course of ACTH in the same daily dosage (25 mg./day)

was given because of almost immediate progression of the fundus changes of retrolental fibroplasia when treatment was stopped. For the last eight days of the second course of ACTH an average daily weight gain of 15.7 gm./day was noted. The urinary "corticosteroid" output was 0.47 mg./24 hours on the fourteenth day of the second course of treatment. Another infant (J. S.) was treated for 25 days with a characteristic inhibition of weight gain during the period of therapy. ACTH was discontinued and rapid increase

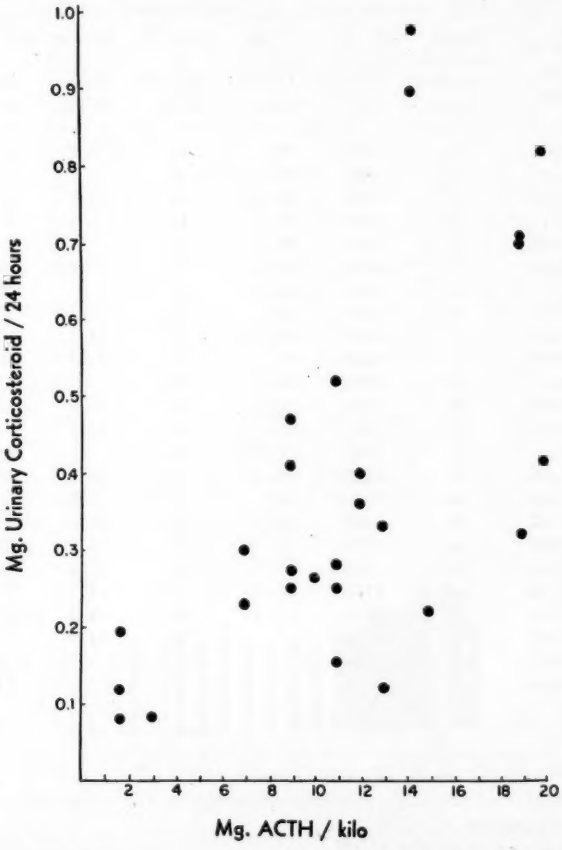

CHART 3. Relationship between daily dose of ACTH and 24 hr. urinary output of formaldehydogenic steroids.

in weight occurred. Therapy was re-instituted seven days later because of progression of the eye lesions; rapid weight gain continued for the first five days of the second course and then was retarded thereafter.

The retarded rate of gain continued uniformly as the dose of ACTH was maintained. In three cases the dose of ACTH was lowered during the course of therapy. Two infants (E. S. and B., first course) were noted to undergo characteristic retardation of weight

gain while receiving ACTH 11 mg./kg./day. As the dose was lowered to 4.5 mg./kg./day (E. S.) and to 9.7 and 7.1 mg./kg./day (B., first course), rapid increase in daily weight gain occurred. This increase became even more marked when ACTH was stopped. One infant (C. C.) showed some retardation of weight gain (15 gm./day as compared with a

TABLE 1

INHIBITING EFFECT OF ACTH ON WEIGHT GAIN

Patient	Birth Wt. (gm.)	Age at Start of ACTH (days)	Wt. at Start of ACTH (gm.)	Total Dose of ACTH (mg.)	Duration of Therapy (days)	Average Daily Wt. Gain (gm.)		
						Before ACTH	During ACTH	After ACTH
H.	1845	15	1920	350	15	8.8	26.4	33.6*
(2nd course)		31	2240	343.75	15		34.6*	32.5
B.	1775	28	2080	284.25	18	32.4	24.1†	50.0
(2nd course)		97	4320	470	13		−26.7‡	129.2
J.F.	1450	29	2370	306	15		− 2.9	29.0
M.	1390	33	1880	187.5	9	26.0	− 7.5	45.7
(2nd course)		50	2100	243.5	11		11.0	44.4
D.	1830	35	2140	72	19	27.1	18.8	23.3
S.	1375	37	2080	558.75	21	24.3	16.0	48.2
J.S.	1110	37	1280	397	25	14.3	11.3	23.2*
(2nd course)		68	1850	580	19		15.0*	Died
A.T.	1340	38	1790	250	14	30.8	17.7	30.0
V.A.	1240	39	1850	286	14	34.2	4.2	53.6
(2nd course)		65	2520	290.25	14		13.1	50.0
T.B.	1500	44	2220	209.25	10	28.2	18.9	42.5
C.C.	1160	46	2030	180	12	29.0	23.0	
K.	850	55	1500	240	14	19.2	3.6	30.0
J.M.	1220	56	2070	314.75	14	16.7	− 1.4	42.7
J.K.	1180	61	2100	312.25	14	32.3	11.7	26.7
E.S.	1120	64	2160	182.75	14	18.7	21.5†	49.2
F.	1360	64	2810	262.25	12	24.5	−23.6‡	44.5
M.R.	920	68	2620	359	20	31.5	7.8	55.8
C.	1675	75	3300	1235	27		− 4.4	Died
L.W.	1330	84	3700	730	20		11.6	13.2§
					Average	24.9	9.3	42.7

* "Rebound" continued into 1st wk. of 2nd course of ACTH.

† Tapering doses of ACTH; weight gain occurred during latter part of treatment period.

‡ Diarrhea during course of ACTH.

§ Diarrhea following cessation of ACTH.

pretreatment rate of 29 gm./day) on ACTH 9.5 mg./kg./day for 6 days. When the dose was lowered to 4.6 mg./kg./day, the daily gain doubled and for the four day period following cessation of ACTH an even more marked increase was noted.

Minimal pitting edema was appreciated in three infants during the latter part of the first week of therapy; this was accompanied by short-lived weight increases. Two infants (F. and B., second course) developed diarrhea on the eighth and ninth days of therapy, respectively. Both promptly lost a considerable amount of weight.

Inhibition of weight gain occurred during the course of treatment using the smallest amount of ACTH, 1.7 mg./kg./day for 19 days. This retardation occurred despite the

fact that only minimal adrenocortical stimulation was achieved with this dose. The 24 hour excretion of urinary "corticosteroids" immediately before treatment was 0.073 mg., and on the fifth day of therapy was 0.12 mg. When ACTH was stopped a short-lived "rebound" weight increase occurred.

Although these infants were irritable and took their feedings with more difficulty while

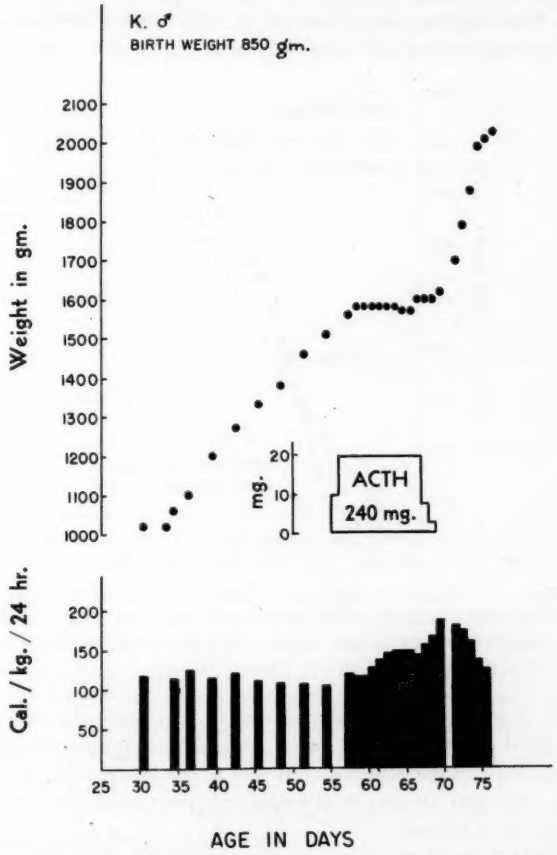

CHART 4. Example of failure of increased caloric intake to influence inhibiting effect of ACTH on weight gain. Period of "rebound" was associated with reduction in caloric intake. Caloric intake/kg. is recorded only for days on which weight of infant was obtained.

receiving the hormone, their total intake of formula was not decreased; many infants became ravenous and demanded increased amounts of formula. An example of the failure of an increased caloric intake to influence the inhibiting effect of ACTH on weight gain is shown in chart 4.

One infant (L. W.) developed diarrhea following completion of the course of ACTH. Rapid weight gain occurred for 10 days, followed by weight loss, so that the average daily weight gain calculated for a period comparable to the period of therapy (20 days) was unimpressive. For two infants (L. W. and J. F.), who were at home after discharge from

Lincoln Hospital, the pretreatment rate of gain was unavailable. One infant (C. C.) was discharged from the nursery four days after completion of therapy and, although rapid gain was evident in this short time, an average post-treatment rate was not calculated. Three infants (J. K., A. T. and D.) had short-lived periods of "rebound" of 5, 4 and 3 days, respectively. Post-treatment rates of gain could not be calculated for two infants who died following therapy. J. S. received cortisone on completing a second course of ACTH and died on the day following cessation of ACTH; C. also received cortisone and died four days after ACTH was stopped and three days after cortisone was stopped. Following

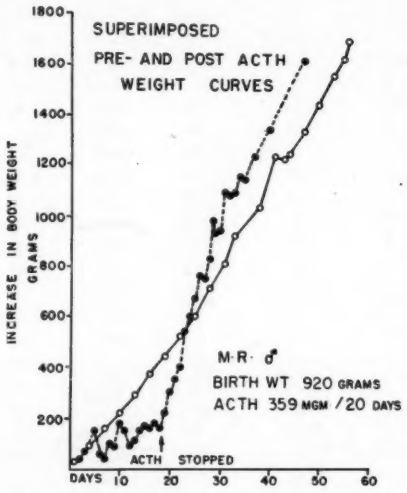

CHART 5. Example of "rebound" weight gain following withdrawal of ACTH. For 12 days following cessation of treatment rate of gain exceeded pretreatment rate. Following this pretreatment rate was resumed. Base-line weight for pre-ACTH curve (open circles) is 1270 gm.; that for post-ACTH curve (solid circles) is 2160 gm.

completion of 16 courses of ACTH administered to 12 infants, the rate of "rebound" weight gain exceeded the pretreatment rate of gain. An example of this phenomenon is shown by the superimposed pre- and post-treatment weight curves in chart 5. The duration of the "rebound" averaged 10 days to 2 weeks, following which the pretreatment rates of daily weight gain were resumed.

2. Length of the Fibula.—Serial measurements of the length of the fibula were obtained at 3 and 4 day intervals in 12 of the 19 ACTH-treated patients. From duplicate RGs of the same leg, taken at a constant tube distance, the length of the fibula was expressed as an average of the diagonals of this rectangular bone, the technic described by Day.[4]

Chart 6 records the superimposed fibula length curves of the treated infants as compared with untreated controls. In all but the one infant who received the smallest dose of ACTH, growth in length of the fibula was retarded during the course of therapy. In the one infant (H.) whose weight gain was not inhibited during the first course of ACTH administration, retardation in growth of the fibula did occur. One infant (M.) received two courses of ACTH separated by an eight day rest period. Inhibition of growth in length of the fibula occurred during the first course of therapy, a "rebound" rapid increase was

noted during the eight day interval without ACTH and was followed by retardation during the second course of therapy. Two infants (H. and J. S.) received double courses of ACTH separated by 36 hour and 6 day intervals. In both these infants minimal increase in length of the fibula occurred during the ACTH-free intervals, in contrast to the marked "rebound" increase in the rate of weight gain that occurred and continued into the first part of the second course of ACTH. One patient (B.) received tapering doses of hormone. "Rebound" in weight gain appeared as the dose was lowered from 11 to 9.7 and 7.1 mg./kg./day. However, increase in length of the fibula did not occur until the dose

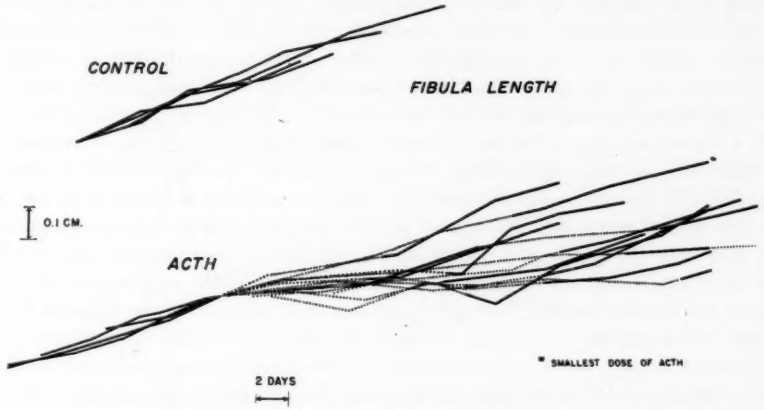

CHART 6. ACTH-induced retardation of growth in length of fibula. Curves are superimposed to day of starting ACTH; broken lines indicate periods of ACTH administration. Retardation was evident in all except infant who received smallest dose of ACTH (1.7 mg./kg./day for 19 days).

reached 3.4 and 2.4 mg./kg./day. The smallest dose of ACTH (1.7 mg./kg./day) resulted in retardation of weight gain but the fibula continued to grow at a normal rate.

"Rebound" increases in rate of growth of the fibula occurred upon final withdrawal of ACTH in all but the nonaffected infant who had received the smallest dose of hormone. Resumption of growth of the length of the fibula was delayed following withdrawal of ACTH in the infant who received one of the most extended courses of ACTH (11 mg./kg./day for 20 days).

No change in the roentgenographic appearance of the bones of the lower leg was apparent during or immediately after therapy.

3. Head circumference.—Serial measurements of the occipitofrontal circumference of the head were obtained in all the treated infants. Retardation of the rate of increase of circumference was noted in all but the infant who received the smallest dose of ACTH. These changes in rate of growth paralleled the fibular measurements. Growth of the head was inhibited in the infant (H.) whose weight gain was not retarded during the first course of ACTH; it then failed to rebound in the short interval between courses of therapy in the same infant. Head growth continued at an uninhibited pace in the infant who received the smallest dose of ACTH. In all except the infant last mentioned, "rebound" increases in the rate of growth of the circumference of the head occurred when administration of ACTH was stopped.

IV. Post-Treatment Status of Infants Treated with ACTH

Following cessation of therapy, all but two of the infants were seen to return rapidly to their pretreatment appearance. Irritability, tachycardia and ravenous appetite subsided within 48 hours after stopping treatment. Papular skin eruptions persisted in several infants for 1 to 2 weeks after withdrawing the drug. It was difficult to judge the time of disappearance of Cushing facies, but the general appearance was approximately normal after 2 to 3 weeks.

Two infants died following completion of hormonal therapy. J. S. received two courses of ACTH, 15 mg./kg./day for 25 days and after a six day interval 16 mg./kg./day for 19 days. On the eighteenth day of the second course of ACTH, cortisone was administered orally in a daily dose of 95 mg./kg./day. On the following day, the dose of ACTH was reduced and stopped, orally administered cortisone was continued. Twenty-four hours after the infant had received his last dose of ACTH, the nurses approached his crib to offer a feeding and found that he was dead. Autopsy failed to reveal the immediate cause of death. C. received approximately 16 mg./kg./day for 27 days. On the twenty-sixth day of ACTH therapy, orally administered cortisone was added in a dose of 66 mg./kg./day. On the following day, the dose of ACTH was reduced and stopped, oral cortisone was reduced to 32 mg./kg./day. Twenty-four hours after receiving the last dose of ACTH and immediately after receiving formula which contained a dose of cortisone, the infant gagged and became cyanotic. Emergency measures were instituted; these included tracheal suction which yielded considerable amounts of aspirated formula. This infant was on antibacterial therapy because of a previous episode of pneumonia which had developed earlier during ACTH administration and had cleared roentgenographically. The antibacterial drugs were continued and the infant was placed in oxygen. Cortisone was discontinued. Improvement in the infant's general condition was noted for the next four days. On the evening of the fourth day, the infant was found dead in his crib. Autopsy revealed an extensive bilateral lobular pneumonia with a considerable amount of tenacious, mucopurulent material in the trachea and major bronchi.

One infant, upon completion of his course of ACTH, developed a severe bout of diarrhea that was presumed to be infectious. Response to the usual methods of therapy was prompt. Another infant was subjected to a hernioplasty 83 days after completion of therapy, and withstood anesthesia and the operative procedure without difficulty. Several infants acquired upper respiratory infections and one developed a urinary tract infection in the weeks and months following cessation of treatment. All these types of stress were handled well.

One infant when examined at the age of 10 months was found to be deaf; there was no response to sound nor to the caloric test of vestibular function. This child did not receive streptomycin at any time. Two infants were examined at the ages of 10 months and 1 year and were found to respond to sound and to have normal vestibular function as determined by the rotation test. The parents of 13 other treated infants were questioned as to the state of auditory acuity and all reported definite response to sound. Psychometric examinations of the treated infants have not yet been obtained. One infant at the age of 1 year appears, clinically, to be seriously retarded in behavior development.

It was difficult to evaluate the long term effects of growth inhibition induced during the course of therapy with ACTH. The standards for "chronological age corrected for prematurity" given by Hess, Mohr and Bartelme,[5] show a wide scatter, and the present

authors' data do likewise. An opportunity presented itself to compare the physical growth of presumedly identical twins (shown in figure 1), with identical blood pedigrees, survivors of a triplet birth. V. W. received no ACTH, L. W. received one of the most extended courses of therapy (11 mg./kg./day for 20 days). Weight, head circumference

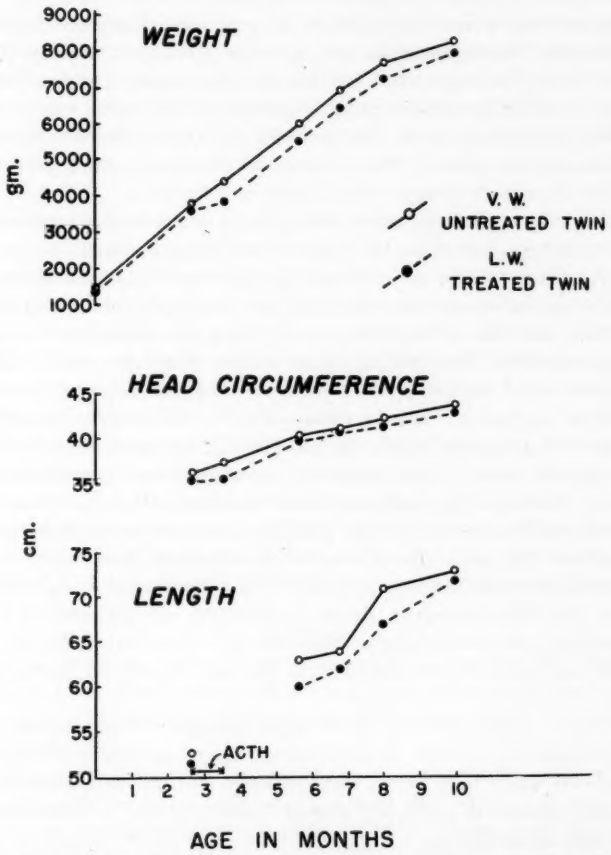

CHART 7. Growth of identical twins, one of whom (L. W.) was treated with ACTH 11 mg./kg./day from 84th through 103rd day of life. At 10 mo. of age, degree of difference in physical dimensions of these twins is same as that before therapy.

and length of these twins from birth to the chronologic age of 10 months are plotted in chart 7. From birth L. W. was the smaller of the pair. The differences between the two infants in their physical dimensions were of the same order at the age of 10 months as they had been before therapy, in spite of L. W.'s episode of ACTH-induced temporary retardation of growth.

Six months after completion of therapy with ACTH, RGs of the lower extremities were obtained in the first treated patient (E. S.) who showed retardation of growth (weight and head circumference) during therapy. In this case films had not been obtained either

before or during therapy. Transverse lines of increased density at the metaphyseal ends of the bone shafts (so-called "growth arrest lines") were present in these RGs. None of the roentgenographic examinations obtained on the follow-up of three other infants showed transverse lines.

Discussion

No published reports could be found of the prolonged therapeutic use of ACTH in premature infants. The hormone has been given to prematures for short periods to determine the status of adrenocortical function and for metabolic studies. Read, Venning and Ripstein[6] described generalized pallor in newborn infants and in one premature infant after receiving single doses of ACTH 2.4 to 20 mg. Levine, Barnett, Bierman and McNamara[7] have observed clinical effects, in normal premature infants given ACTH, that were similar to those in the present authors' experience.[8]

Observations of premature infants in this series have shown that profound changes in their behavior and appearance can be expected when doses of ACTH in excess of 5 to 10 mg./kg./day are used. Doses up to 20 mg./kg./day were tolerated, and reversal of the signs of acute hyperadrenocorticism occurred upon final withdrawal of the hormone. The two deaths that took place in this series are disturbing. One death (of C.) was attributed to pneumonia following fortuitous aspiration of food. The other (of J. S.) occurred 24 hours after cessation of ACTH, on the third day of orally administered cortisone, and for want of another explanation must be presumed to be related to the use of these drugs. In the absence of laboratory studies at this point in the treatment of this infant, no postulate is offered to explain the mechanism of sudden death. Both experiences emphasize that when prolonged hyperadrenocorticism has been induced in a premature infant, he must be carefully observed for the possibility of a sudden dramatic change in his clinical condition. The exact role of cortisone in relation to these deaths is not clear.

As has been emphasized recently by Rhoads,[9] and experienced in this study, the usual symptoms of acute infection may be absent in individuals who are receiving ACTH, while bacterial infection continues unabated. Response to antibacterial drugs may occur even while ACTH continues to be administered, as was also experienced during the course of this study.

The positive correlation between body weight and the 24 hour urinary excretion of formaldehyde-liberating steroids in untreated premature infants is in agreement with other studies,[10-12] which have shown that premature and full term newborn infants excrete increasing amounts of chemically assayed "corticosteroids," 17-ketosteroids and glucocorticoids with increasing age.

Determination of "corticosteroid" excretion in response to varying doses of ACTH showed marked individual variation. From the data obtained on the present series of treated infants, there is some suggestion that maximal stimulation of the premature infant's adrenal cortex can be achieved with daily doses of 15 to 20 mg./kg.

Moon[13] in 1937 described the effects of an adrenocorticotrophic extract of the anterior pituitary administered to immature gonadectomized rats. Weight gain of the treated animals was found to be retarded as compared with controls, whereas the weight of the adrenals was markedly increased. Subsequently, Evans, Simpson and Li[14] demonstrated that purified adrenocorticotrophic hormone retarded weight gain of normal and gonadectomized immature rats, caused weight loss when administered to normal mature rats, and had no effect on the rate of weight gain when injected into salt-maintained, adrenalectomized, immature rats.

The effects of ACTH on the osseous system of normal rats have been studied by Becks, Simpson, Li and Evans.[15] Retardation of osteogenesis and chondrogenesis was recorded. These effects of administered ACTH were compared with hypophysectomy,[16] which produced complete arrest of osteogenesis, and with the effect of ACTH given to adrenalectomized rats, which produced no histologic difference as compared with controls. ACTH antagonized the action of growth hormone when both were injected into hypophysectomized rats. Simpson, Asling and Evans[17] obtained roentgenographic studies of intact and hypophysectomized rats treated with ACTH for sufficient periods to produce growth stasis. These studies indicated no appreciable effect on skeletal maturation. Baker and Ingle[18] have shown retardation of chondrogenesis and osteogenesis in the bones of ACTH-treated adult rats. Force-fed diets high in carbohydrate, fat and protein did not modify these inhibitory influences.

The premature infants treated in the present series showed growth retardation comparable to that of the experimentally treated rats. The "rebound" phenomenon observed upon cessation of treatment can be compared with a similar excessive rate of growth observed by Jackson[19] in rats which were re-fed after a long period of food restriction. Winter, Silber and Stoerk[20] did not observe a comparable "rebound" after producing growth inhibition in rats by the use of cortisone. Although weight gain on stopping cortisone was three times the rate of controls of the same age, it was not greater than controls of the same weight.

The relationship of dosage of ACTH to growth retardation cannot be accurately determined from this small group of treated infants. It seems likely, however, that a daily dose in excess of 5 mg./kg. is necessary to produce marked growth inhibition.

Terminal animal experiments shed no light upon the long-term growth effects of a period of ACTH-induced retardation. At the present time, it is impossible to judge the long-term effects of therapy with ACTH in the present series of premature infants.

Summary

Premature infants who received more than ACTH 5 mg./kg./day became hyperirritable and ravenous. Many became pallid immediately after injection of the hormone. During the course of treatment infections which appeared could be controlled with antibacterial therapy.

Untreated premature infants excreted increasing amounts of chemically assayed urinary "corticosteroids" with increased body weight. Under the influence of doses of ACTH in excess of 5 mg./kg./day the urinary excretion of "corticosteroids" increased significantly.

Retardation of growth occurred during the administration of more than 5 mg. ACTH/kg./day. "Rebound" increase in growth took place upon cessation of hormonal administration.

Acknowledgment

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SPANISH ABSTRACT

Inhibición del Crecimiento y Otros Efectos del ACTH en Niños Prematures

Los autores administraron ACTH a 19 prematuros con fibroplasia retrolental, con el propósito de inhibir el progreso proliferativo vascular de la afección. La edad de los pacientes al comienze del tratamiento osciló entre 15 y 84 dias. La ACTH fué administrada en cursos de 9 a 27 dias con dósis que variaron entre 1.7 a 20 miligramos por kilogramo de peso, por día. Cinco pacientes recibieron dos cursos de ACTH. Dos prematures fallecieron siguiente a la terminación del tratamiento.

Los siguientes sintomas aparecieron durante la administración del ACTH: irritabilidad nerviosa, taquicardia, apetito excesivo, erupciones papulares de la piel, edema, regurgitación, palidez después de la inyección y redondez de la cara (Cushing facies). Infecciones intercurrentes, las cuales respondieron al tratamiento antibacterial, ocurrieron durante el tratamiento hormonal. La excreción urinaria de los esteroides formaldehydogenicos aumentó marcadamente durante la administración del ACTH.

El promedio de ganancia de peso diario de los prematures tratados, calculado con periodos comparables antes, durante y después del tratamiente fueron de 24.9, 9.3 y 42.7 grames por día, respectivamente. Aumentos en la ingestión de calorias durante el tratamiento no modificó la influencia inhibidora del ACTH sobre la ganancia de peso diario. Siguiente, a la terminación del tratamiento se observó un aumento rapido (rebound) de los promedios de ganancias de peso diario.

Determinaciones radiograficas seriadas de la longitud del huese peroneal fueron obtenidas a intervalos de 3 a 4 días, en 12 prematuros tratados con ACTH. El crecimiento de este hueso estuvo detenido durante el tratamiento, observandose un crecimiento rapido (rebound) del hueso a la terminación del tratamiento hormonal. Determinaciones seriadas de la circumferencia occipitofrontal de la cabeza reveló cambios en el crecimiento durante y siguiente a la cesación del tratamiento, los cuales fueron paralelos a los cambios observados en el hueso peroneal.

Se comparó el crecimiento fisico de dos gemelos idénticos, de los cuales uno solo fué tratado con ACTH. Las diferencias en las dimensiones fisicas de ambos niños fueron del mismo orden a la edad de diez meses, tales como habian sido antes del tratamiento.

3975 *Broadway*

COARCTATION OF THE AORTA AS A CAUSE OF DEATH IN EARLY INFANCY

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COARCTATION of the aorta may cause cardiac failure and death in young infants. While this fact has been widely accepted, the stated reasons need to be re-evaluated. Blackford[1] and Abbott[2] considered that coarctation of the aorta in infants is not of importance, because the so-called infantile type (the coarctation lying proximal to the ductus arteriosus) is usually associated with other grave anomalies of the heart; and the so-called adult type (the coarctation lying distal to the ductus arteriosus) is probably not a common cause of disability to infants and young children. That the so-called infantile type of coarctation of the aorta may be the only significant anomaly in a given patient is attested by the reports of Calodney and Carson,[3] Benkwitz and Hunter,[4] and Blackford,[1] who found 73%, 92% and 75%, respectively, of their patients to be free of other associated grave anomalies. A high fatality rate in these series of cases was attributed to cardiac failure, although an acute infection frequently was thought to precipitate or accelerate the decompensation.

Interest in intrathoracic vascular abnormalities of the infant has been renewed because surgical thoracic exploration at this period of life has now become practicable and not attended with prohibitive mortality rates. Since obstruction of the aorta can cause death in early infancy and since surgical intervention could correct or improve the underlying abnormality, a review of certain cases of coarctation of the aorta in infants is justified. By this means, a better understanding of the various types of coarctation and their pathologic physiology can be achieved.

Coarctation of the aorta may occur proximal to, distal to, or opposite the ductus arteriosus. The location of the obstruction of the aorta and the degree of patency of the ductus arteriosus determine the resultant circulation and the stress on the left and right ventricles. Three instances of coarctation of the aorta opposite the closed or closing ductus arteriosus, with inadequately developed collaterals resulting in failure of the left ventricle during early infancy, are herein reported.

CLINICAL FEATURES

Three infants were admitted to the hospital under the care of the Mayo Clinic and died at the ages of 6, 7 and 25 wk., respectively. In each case the history of the pregnancy was not remarkable. Two of the infants were delivered spontaneously, and 1 was born by cesarean section because of dystocia. Each infant was apparently normal in the immediate postnatal period.

The first baby began to wheeze within 1 wk. after birth. Shortness of breath and a cough were present by the age of 3 wk. At 4 wk., dyspnea was marked and cyanosis was noticed. When this infant was admitted to the hospital, the cyanosis was relieved by the administration of oxygen but it recurred with crying or feeding. Rales were present in both lungs. A precordial systolic murmur was heard. The liver was not enlarged. No notation of femoral arterial pulsations was made on the record. Roentgenographic examination disclosed marked enlargement of the heart, the left border extending almost to the thoracic wall (Fig. 1a). Electrocardiographic examination demonstrated

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biphasic QRS complexes (Fig 1b). The infant was given digitalis in therapeutic doses, and oxygen was administered constantly with resultant improvement for a few days. However, dyspnea then increased, cyanosis became more marked, and death occurred 7 days after admission at the age of 6 wk.

The second infant was considered to be normal until the day before admission to the hospital, at the age of 7 wk., when she refused feedings, became fussy and cried continuously. The following

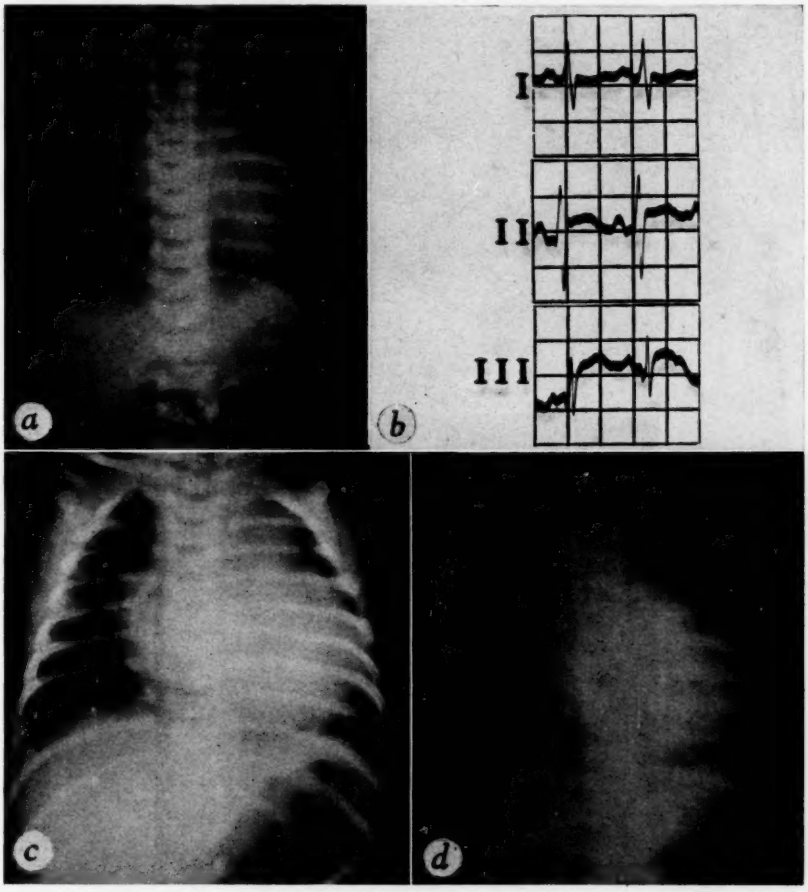

FIG. 1a. (Case 1) RG of thorax. b. (Case 1) ECG. c. (Case 2) RG of thorax. d. (Case 3) RG of thorax.

day heavy breathing and cyanosis were observed. Examination revealed dyspnea and cyanosis and evidence of pulmonary emphysema. No cardiac murmurs were heard. The presence or absence of femoral arterial pulsations was not recorded. RGs of the thorax confirmed the presence of emphysema and disclosed enlargement of the heart (Fig. 1c.) Because of the emphysema and the sudden onset of symptoms, aspiration of a foreign body was suspected. Bronchoscopy was performed with negative findings. The infant died 24 hr. after admission.

The third infant progressed satisfactorily until the age of 2 mo. when he refused his feedings and failed to gain weight. Changes in his formula resulted in temporary improvement, but he did not

thrive and was sent to the hospital for study at the age of 25 wk. Physical examination disclosed malnutrition and an enlarged heart with a rapid rate (160 beats/min.). No notation was made concerning femoral arterial pulsations. Roentgenographic examination of the thorax revealed a large, globular cardiac shadow and a shadow suggesting pneumonia at the apex of the right lung (Fig. 1d). The baby rapidly became dyspneic, cyanosis and fever developed and he died within 24 hr. after admission to the hospital.

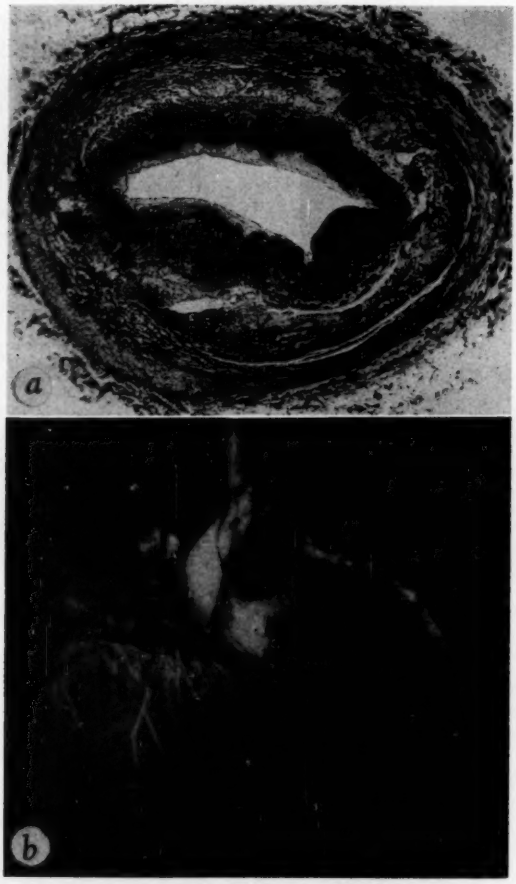

FIG. 2. (Case 1) a. Section of ductus arteriosus. There is thickening of media and intima with marked luminal narrowing indicating normal process of closure (Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissues stain ×18). b. Exterior of heart and great vessels. Heart is greatly enlarged. Opposite aortic attachment of ductus arteriosus is typical concavity of superior wall of aorta indicative of coarctation. Photomicrograph of this lesion is shown in Fig. 3a.

PATHOLOGIC FEATURES

The essential necropsy findings were similar in the 3 cases and will be described together. Opposite the aortic end of a closed or closing ductus arteriosus (Fig. 2a), there was a clearly defined concavity involving the superior, anterior and posterior walls of the aorta. In this regard the external appearance of the aorta was typical of that seen in coarctation of the aorta (Fig. 2b).[5] At the level

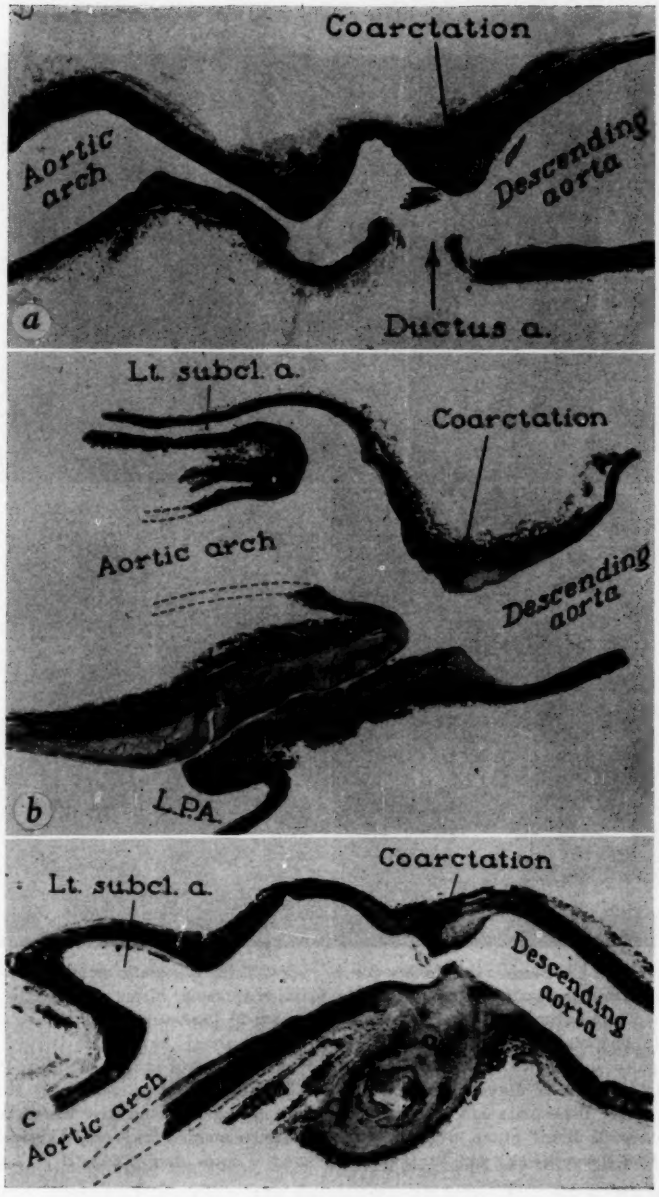

FIG. 3. Coronal sections of aorta through aortic arch, aortic isthmus, zone of coarctation and descending aorta (Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain ×6). a. (Case 1) Coarctation at level of aortic mouth of ductus arteriosus. Artefact is present at site of ductus arteriosus which was closing (see Fig. 2a). Coarctation is represented by curtain-like protrusion of media of superior wall of aorta into lumen, producing diaphragm-like aortic obstruction opposite mouth of ductus arteriosus. b. (Case 2) Coarctation opposite aortic mouth of obliterating ductus arteriosus. c. (Case 3) Coarctation at level of aortic mouth of obliterated ductus arteriosus. Lumen of ductus arteriosus was completely obliterated at both aortic and pulmonary mouths but was minimally patent in illustrated midportion.

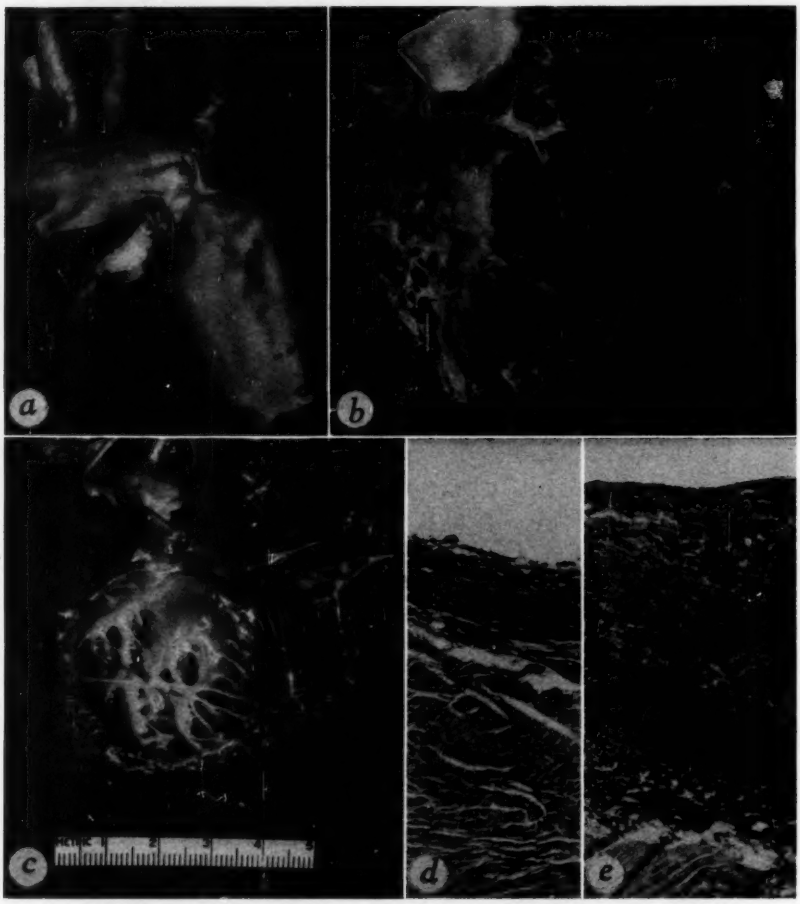

FIG. 4a. (Case 2) Thoracic aorta. Coarctation is evident at level of aortic mouth of ductus arteriosus. Ostia of intercostal arteries do not appear to be abnormally dilated as would be expected if adequate collateral channels had been developed. b. (Case 2) Interior of hypertrophied and dilated left ventricle. Endocardium is opaque and thickened. Aortic valve is bicuspid. c. (Case 3) Interior of hypertrophied and dilated left ventricle. Endocardium is gray and opaque. d. (Case 3) Section of left ventricle. There is thickening of endocardium by collagen and particularly by elastic tissue (Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain ×60). e. (Case 3) Section of left atrium. There is marked fibrous endocardial thickening (Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain ×60).

of the concavity the aortic wall was thickened and in this way protruded into the lumen of the aorta causing the lumen to be eccentric and narrow. The microscopic appearance of the aorta at the level of the deformity was characteristic of that seen in coarctation. The media of the superior, anterior and posterior portions of the aortic wall showed localized thickening, and protruded curtain-like into the aortic lumen. The lower wall of the aorta, that is, the wall into which the ductus arteriosus inserted, was not deformed (Fig. 3). In no case were the ostia of the intercostal arteries particularly dilated and they seemed to be narrower than would be expected in the event that

adequate collateral circulation had developed to by-pass the coarctation. In each case the collateral channels were interpreted as being inadequate (Fig. 4a).

There was marked cardiac enlargement, caused particularly by hypertrophy of the left ventricular wall (Figs. 2b and 4b and c). The endocardium of the left ventricle and of the left atrium were gray and thickened. Microscopically these layers were composed largely of collagen and elastic tissue (Fig. 4d and e). In each case the vascular connections with the heart were normal and the coronary arteries arose from the aorta. The ventricular septa were intact. Each heart exhibited a probe-patent foramen ovale but no true atrial septal defect. The details of the pathologic findings in each case are recorded in table 1.

In each case left ventricular failure was considered to be the immediate cause of death. Pulmonary congestion was present in each instance.

TABLE 1

PATHOLOGIC FEATURES IN 3 INFANTS WITH COARCTATION OF AORTA OPPOSITE CLOSED OR CLOSING DUCTUS ARTERIOSUS WITH INADEQUATE COLLATERALS

	Case 1	Case 2	Case 3
Age at time of death, wk.	6	7	25
Sex	Male	Female	Male
Wt. of heart, gm.	75	65 (est.)	90
Estimated normal cardiac wt., gm.	21	21	31
Thickness of right ventricle, cm.	0.5	0.4	0.5
Thickness of left ventricle, cm.	0.8	1.0	1.2
Diameter of ascending aorta, mm.	7.5	6.5	7.5
Diameter of aortic arch, mm.	3.0	4.0	5.0
Diameter of aortic lumen at coarctation, mm.	2.0	1.5	1.5
Diameter of descending aorta, mm.	4.5	3.5	6.5
Aortic valve	Bicuspid	Bicuspid	Normal
Liver, ratio of actual wt. to estimated normal weight, gm.	180/132	145/132	250/160

COMMENT

Aortic coarctation may be classified on the basis of the relation of the constriction to the ductus arteriosus and also as to whether the ductus is patent or closed. As regards the location of the coarctation three categories are apparent: coarctation proximal to the aortic mouth of the ductus arteriosus, coarctation at the level of the ductus arteriosus, and coarctation distal to the ductus arteriosus. We assume that aortic coarctation exists before birth and so we consider that the relative positions of the coarctation and the ductus arteriosus have major influences in the development or failure of development of a collateral circulation before birth. This fact has been pointed out by Ballantyne[6] and reemphasized by Edwards and associates,[7] by Calodney and Carson[3] and by Olney and Stephens.[8]

In the normal fetus most of the left ventricular output is probably distributed to the great vessels arising from the aortic arch; accordingly, little left ventricular blood flows through the isthmus of the aorta into the descending aorta. The major portion of the blood in the descending aorta is derived through the ductus arteriosus from the right ventricle. Under these circumstances of adequate supply of blood to the descending aorta, collaterals as seen in coarctation of the aorta do not develop. These normal phenomena are quite in contrast to those which exist in the fetus with coarctation below the aortic mouth of the ductus arteriosus. In this condition it is apparent from figure 5a

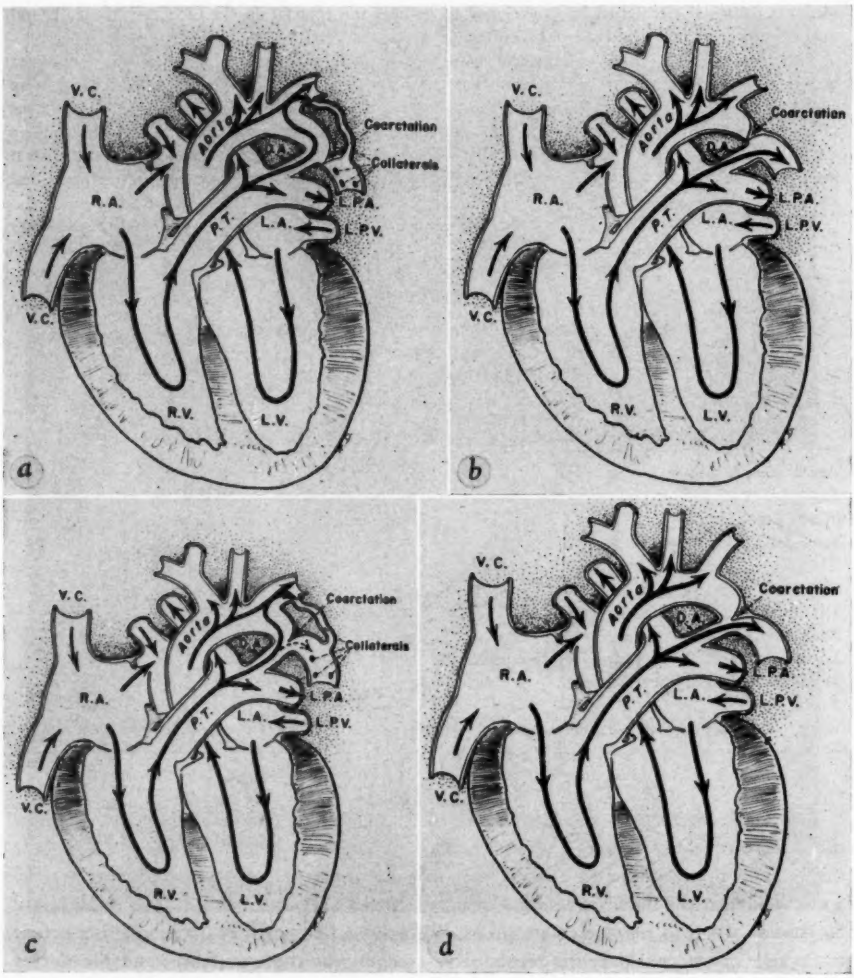

FIG. 5. Fetal circulation in various types of aortic coarctation. Whether adequate collaterals will develop to by-pass the coarctation depends upon position of coarctation with respect to aortic mouth of ductus arteriosus. a. Coarctation lies distal to aortic mouth of ductus arteriosus. Collateral channels must develop in fetus if intrauterine life is to be maintained. b. Coarctation proximal to aortic mouth of ductus arteriosus. Circulation is similar to that present in normal fetus. There is no stimulus for development of collateral channels during fetal life. c. Hypothetic case of coarctation at level of aortic mouth of ductus arteriosus with predominant blood flow in direction of aorta proximal to coarctation. Circulation is similar to that of condition illustrated in a. Collateral channels should develop. d. Coarctation of aorta at level of aortic mouth of ductus arteriosus with predominant flow into descending aorta. Existing dynamics are similar to those of condition illustrated in b. Adequate collateral channels do not develop. This type of circulatory phenomenon seems to have existed in 3 cases reported herein.

that both the left ventricle, by way of the ascending aorta, and the right ventricle, by way of the ductus arteriosus, feed blood to the aorta proximal to the coarctation. Were no collaterals developed to by-pass the coarctation, little blood would reach the descending aorta and in all probability there would be inadequate flow of blood to the placenta. Such a fetus probably would not live to full maturity. The fact that fetuses born with coarctation distal to the ductus arteriosus have lived to full maturity is in itself indication that adequate flow of blood had occurred in the descending aorta. Such a flow must of necessity have depended upon the presence of collaterals. It may be concluded, therefore, that in the subject with coarctation distal to the ductus arteriosus, collaterals by-passing the coarctation develop during fetal life. In such an individual closure of the ductus arteriosus after birth has no disturbing influence upon the systemic circulation since the collaterals are already in existence.

In 1950 a comprehensive report on the clinical manifestations of symptomatic coarctation in early infancy was presented by Buchs.[9] He adopted the view that collaterals do not develop before birth. He based his conclusions on the assumption that systolic murmurs in coarctation are dependent upon blood flow through collaterals. Since the onset of systolic murmurs in his cases was delayed, he concluded that the development of collaterals was delayed and consequently postnatal. It has been shown by Burchell[10] that, while blood flow through collaterals may give rise to systolic murmurs, the presence of systolic murmurs in coarctation need not be that of blood flow through collaterals but may originate at the aortic valve. Buchs' contention that collaterals do not develop before birth does not seem adequately supported by the evidence which he presented.

The fetus with coarctation proximal to the ductus arteriosus has circulatory characteristics which are similar to those of the normal fetus and which differ from those of the fetus with coarctation distal to the ductus arteriosus. During fetal life the presence of aortic coarctation proximal to the ductus arteriosus alters the circulation little, if any, from that in normal fetuses (Fig. 5b). In this particular malformation, as in the normal individual, the right ventricle is able adequately to supply blood to the descending aorta. Since this part of the aorta is properly filled, stimuli for the development of collaterals are wanting and, as in the normal, collaterals do not develop. It follows that at birth little or no collateral circulation is present to by-pass the aortic coarctation. As long as the ductus arteriosus remains patent the descending aorta can derive blood from the right ventricle by way of the ductus arteriosus. In such a case the right ventricle maintains its fetal function of being a systemic ventricle. The right ventricular and pulmonary arterial pressures are comparable to the systemic arterial pressures. There is a decreased oxygen saturation of the arterial blood in the lower extremities.[7, 11–15] If in this type of coarctation of the aorta the ductus arteriosus closes after birth, the main source of blood to the descending aorta is lost. Since collaterals had not developed, there is a severe obstruction to blood flowing from that part of the aorta proximal to the coarctation. Before adequate collaterals can be formed, left ventricular strain and decompensation may develop and cause death.

When the coarctation lies opposite the aortic mouth of the ductus arteriosus it appears that one of two possible effects upon the development of collaterals may exist. These effects may depend upon the angle at which the ductus enters the aorta. It is hypothetically possible that in some such cases little flow would occur through the ductus into the aorta distal to the coarctation and that most of the ductal blood would flow into the aorta

proximal to the coarctation (Fig. 5c). Under these circumstances the circulatory characteristics would be exactly like those in cases wherein the coarctation lies distal to the aortic mouth of the ductus. Collaterals would be expected to develop.

In other patients with coarctation opposite the aortic mouth of the ductus arteriosus it seems probable that the majority of the blood which flows through the ductus during fetal life enters the descending aorta. Under these circumstances the functional character-

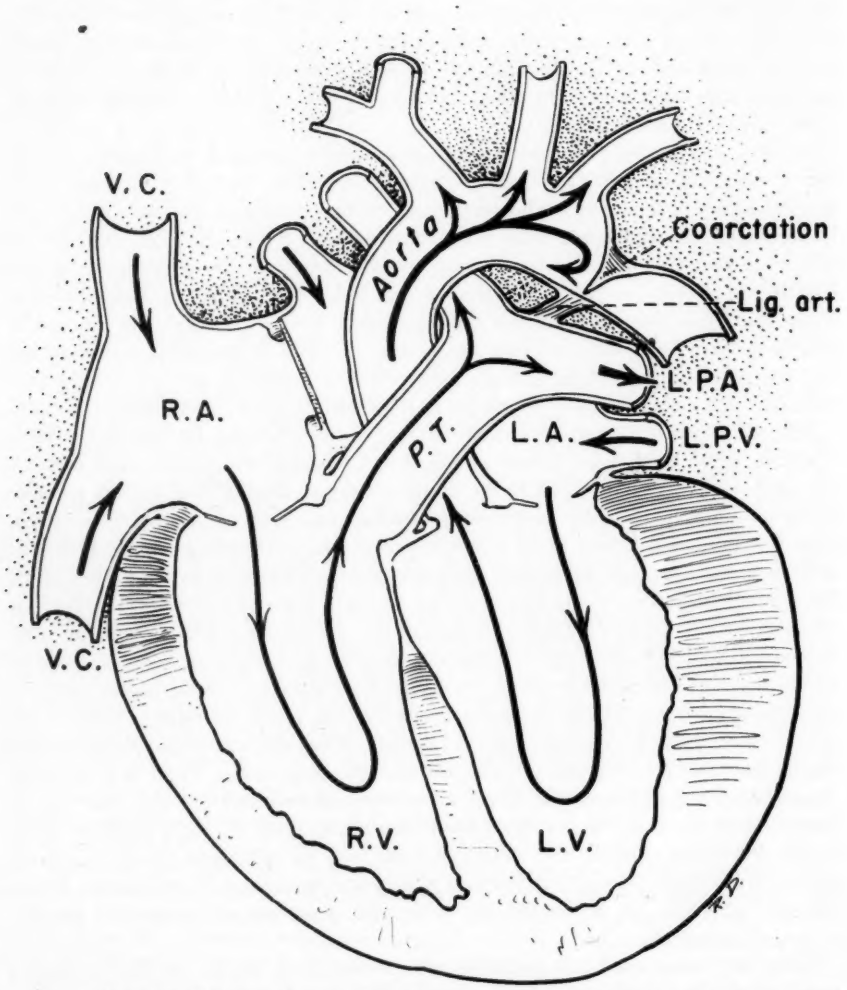

FIG. 6. Postnatal circulation in coarctation of aorta opposite aortic mouth of ductus arteriosus in which blood flow during fetal life was through ductus arteriosus into descending aorta (Fig. 5d). No adequate collateral channels develop during fetal life. After closure of ductus arteriosus coarctation with inadequately developed collaterals causes obstructive hypertension proximal to coarctation.

istics would be identical to those in the cases wherein the coarctation lay proximal to the ductus arteriosus (Fig. 5b and d). With the descending aorta being adequately supplied by the right ventricle there would not be the stimuli for the development of collaterals. A fetus with such a malformation would develop normally. After birth, however, when the ductus arteriosus closed the descending aorta would fail to be supplied by the right ventricle and the inadequately developed collaterals would be incapable of carrying a substantial proportion of the left ventricular output (Fig. 6). An obstructive hypertension would result. This, in turn, would cause left ventricular strain and hypertrophy and ultimately left ventricular failure. Like opinions were expressed by Gross.[16]

The importance of collateral circulation is objectively emphasized by the recent work of Olney and Stephens. They showed by means of intra-arterial iodopyracet (diodrast) studies that in a group of children hospitalized for cardiac decompensation accompanying uncomplicated coarctation of the aorta there was a paucity or absence of demonstrable collateral circulation. In a comparable group of infants without cardiac failure, collateral channels were distinctly outlined. It is realized that collaterals in this type of case could develop after birth if the infant survives the period of left ventricular strain.

There is general belief that the patient born with coarctation of the aorta proximal to the patent ductus arteriosus has a poor chance of survival. This is often attributed to the supposition that associated malformations are the basic cause of early death in such cases. Few have stated that the early death may result from closure of the ductus. In the presence of inadequate collaterals, left ventricular failure seems to be the mechanism by which early death is brought about. This chain of circumstances gives due importance to the coarctation.

The endocardial sclerosis present in the cases reported here are considered of secondary nature and a consequence of left ventricular dilatation incident to failure.

The three cases described in this communication seem to be examples of the last type of coarctation described, that is, in each there was coarctation of the aorta opposite the ductus arteriosus. The ductus was closed or closing, and there seemed to be inadequate collaterals to by-pass the coarctation. In each case there was pronounced left ventricular hypertrophy and ultimately lethal left ventricular failure.

The salient clinical features in these three cases were the same. After early normal progress, feeding difficulties occurred. Dyspnea and then cyanosis followed in rapid order. Death occurred shortly after illness became apparent. The proper clinical diagnosis was not suspected, because the character of the femoral arterial pulsations was not noted, and no recording of the blood pressure of the arms was made. It is suggested that the results of palpation of the femoral arterial pulses might have led to the correct clinical diagnosis.

It seems that therapy in cases such as these must be prompt and directed toward relief of the obstruction to aortic flow caused by the coarctation with inadequate collaterals. Resection of the coarctation and end-to-end aortic anastomosis as advocated by Calodney and Carson[3] and by Olney and Stephens[8] seem appropriate to relieve the condition which otherwise may prove rapidly lethal. When symptoms become apparent they are those of the failing left ventricle. Burchell[10] has suggested that temporary relief of left ventricular strain before and during an operation upon the aorta could be afforded by artificially creating a collateral channel in the form of anastomosis of a radial artery with a femoral artery by means of a plastic tube or similar device.

SUMMARY

This is a report of three cases in each of which an infant exhibited coarctation of the aorta at the level of a closed or closing ductus arteriosus. In all cases the collateral channels were poorly developed. It appears from the available evidence that death resulted from left ventricular congestive failure secondary to an obstructive hypertension.

The development of collaterals to by-pass a coarctation of the aorta seems to depend upon the relation of the aortic coarctation to the aortic mouth of the ductus arteriosus. When the coarctation lies distal to the ductus, collaterals develop. When the coarctation lies proximal to the ductus, adequate collaterals do not develop before birth. When the coarctation lies opposite the aortic mouth of the ductus arteriosus, the development of collaterals during fetal life seems to depend upon the direction that the blood flowing in the ductus arteriosus takes. When the flow is into the aorta proximal to the coarctation, collaterals would be expected to develop; while when the ductal flow is into the descending aorta, adequate collaterals would not be expected to develop in the fetus. The three cases reported fall into the latter category.

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SPANISH ABSTRACT

La Coartación de la Aorta Como Causa de Mortalidad en la Infancia

Los autores hacen un análisis de tres niños que murieron con una insuficiencia ventricular izquierda a consecuencia de la coartación de la aorta con circulación colateral inadecuada. En los tres casos la

coartación se encontraba situada opuestamente a un conducto arterioso casi o completamente obliterado. En esta anomalia, la posición de la coartación con respecto a el sitio de entrada de el conducto arterioso en la aorta, determina o nó el desarrollo temprano de una circulacion colateral adecuada durante el periodo fetal. Si la posición de la coartacion es distal en relacion con el conducto arterioso, necesariamente se desarrollaran vasos sanguineos colaterales si el feto sobrevive. Si la posición de la coartacion es proximal a el sitio de entrada del conducto arterioso, la formación de circulación colateral es minima ó ninguna durante el periodo fetal. En este último tipo de coartación de la aorta con circulacion inadecuada, la obliteración del conducto arterioso produce la sobrecarga e insufiencia del ventriculo izquierdo. Si el niño sobrevive, la circulación colateral puede desarrollarse después del nacimiento. En el grupo de casos que presentan la coartacion situada opuestamente a la entrada del conducto arterioso, el desarrollo de circulación colateral puede ocurrir en algunos casos y estar ausente en otros. Parece ser que el desarrollo de circulación colateral en estos casos depende de la dirección predominante de la corriente sanguinea de el conducto arterioso hacia la aorta. Cuando la corriente sanguinea predomina hacia la aorta descendente, los vasos colaterales no se desarrollan. En aquellos casos en los cuales la dirección de la corriente sanguinea es predominantemente hacia la region próximal de la aorta, la circulación colateral se desarrolla durante el periodo fetal.

La condición de estos tres pacientes reportados en este estudio constituye ejemplos de coartación de la aorta situada opuestamente a el conducto arterioso y en la cual la formación de circulación colateral fué inadecuada. Los efectos de esta anomalia en presencia de un conducto arterioso casi o completamente obliterado fueron: hipertensión obstructiva, sobrecarga del ventriculo izquierdo, y finalmente, insuficiencia ventricualar izquierda. La palpación de los pulsos femorales es indispensable para el diagnóstico clinico correcto de estos casos.

Mayo Clinic

MUMPS MENINGOENCEPHALITIS

With Special Reference to the Use of the Complement-Fixation Test in Diagnosis

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MENINGOENCEPHALITIS as a manifestation of infection with mumps virus has long been recognized through clinical and epidemiologic observations. The meningoencephalitis may be preceded, accompanied or followed by involvement of the salivary glands. When parotitis occurs before or simultaneously with meningoencephalitis, a clue as to the nature of the infecting agent is obtained immediately. But when meningoencephalitis constitutes the only presenting feature the correct diagnosis cannot be made without the aid of appropriate specific laboratory tests, since other infectious agents may give rise to a similar clinical picture. It is true that in the past some of these cases could be properly classified by subsequent development, after characteristic incubation periods, of typical mumps in siblings or nursing personnel.[1, 2] However, this simply constituted circumstantial evidence which, furthermore, was so late in appearing as to be of academic interest only.

With the advent of specific laboratory technics, the diagnosis of mumps meningoencephalitis even in the absence of salivary gland involvement has become a routine procedure. As in other virus infections such a diagnosis may be based either on the isolation of the etiologic agent or on the demonstration of the development of specific antibodies in response to the illness.

As to the isolation of virus, it had been shown by Habel[3] and by Levens and Enders[4] that mumps virus could be adapted to the chick embryo after it had been passaged in monkeys. Subsequently, it has been demonstrated that virus can be transmitted directly from the saliva of patients with parotitis to the amniotic cavity of chick embryos.[5–10] However, an incubation period of at least five days is required before the virus can be detected in the amniotic fluid or membrane by complement fixation[3] or, more simply, by the hemagglutination phenomenon.[4] Furthermore, attempts to isolate virus from saliva have not been successful with regularity when only single specimens were studied[5, 6, 8] and, if the results of various authors are combined, it is obvious that isolation has been successful in no more than about two thirds of the cases. Under conditions of experimental infection where the time of exposure was definitely known, and specimens of saliva were obtained at frequent intervals, virus was isolated from all patients.[11] Even so, it was noted that on consecutive days negative results were obtained in between positive isolations. This would indicate that virus is excreted intermittently, or, more likely, that the available technics are not sufficiently sensitive. Mumps virus has been isolated also from the spinal fluid of patients with meningoencephalitis,[7, 10, 12, 13] but again with irregular success.

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Thus, although isolation of the virus constitutes the most convincing proof of the etiology of the disease, failure of isolation proves nothing.

As regards the diagnosis by serologic means, a number of methods have been described: the complement fixation test with single antigens,[14] inhibition of hemagglutination,[10] agglutination of red cells "sensitized" by virus[15] and prevention of hemolysis caused by the agent.[16] All these technics have been shown to be suitable for the demonstration of the development of specific antibodies, when sera obtained during the acute and convalescent stages of the disease are compared. It is inherent in this type of testing, because of the dependence on a convalescent serum, that about two weeks' time elapses before a diagnosis can be made.

Further progress was made when it was shown[17] that chick embryos infected with mumps virus contained two specific complement fixation antigens. One is linked with the virus particle, called V antigen; the other, a small component, is termed soluble or S antigen. Antibodies to these two antigens usually appear at different rates in patients, the anti-S preceding the anti-V antibody. This phenomenon provides a method for the early diagnosis of the various manifestations of mumps even in the absence of salivary gland involvement. If a serum taken during the acute stage of illness reveals an appreciable titer of antibodies against S but a low titer or no antibodies against V, a presumptive diagnosis of infection with mumps virus can be made on a single serum specimen. This presumptive diagnosis should be confirmed subsequently by the demonstration of an antibody rise, particularly in anti-V. During convalescence both antibodies reach high levels, but in subsequent months and years both decrease again, antibodies to S at a faster rate, usually, than those against V.

The differential use of V and S antigens has proved of particular value in the early diagnosis of mumps meningoencephalitis, in the absence of other signs of mumps. In the course of several years, the Virus Diagnostic Laboratory at The Children's Hospital of Philadelphia has had the opportunity of assisting in the diagnosis of 85 cases of mumps meningoencephalitis, of which approximately one half were not accompanied by involvement of the salivary glands. It is the aim of this communication to analyze these cases particularly with respect to the value of the S and V tests in the serologic diagnosis and to compare the clinical and routine laboratory findings, as provided by the various hospitals in which the patients were treated, with those reported in the recent literature.[13,18,19] The number of patients included in the analysis of the individual aspects is variable depending on the completeness of the available records.

Results

Epidemiologic and Clinical Aspects: Parotitis, although observed throughout the year, shows a seasonal increase during the winter and early spring. Cases of mumps meningoencephalitis have been diagnosed in each month of the year, with somewhat greater frequency between March and July.

Of the 85 patients in this series, 83.5% were males, a confirmation of observations made by other investigators.[13, 18] This preference is striking since both sexes appear to be equally susceptible to the virus as evidenced by similar incidence of parotitis.

The patients ranged in age from one year to 27 years. The 5 year old children alone comprised 23% of the group, and 88.4% were 8 years old or younger. It should be noted, however, that the majority of specimens were submitted by pediatricians or from pediatric hospital services. Thus, the statistics are weighted in favor of the younger age groups.

Nevertheless, in other studies the younger age group likewise was predominant.[13, 18]

Five patients in this series gave histories of neuropathology in the past. One child was mentally retarded; a second gave a history of repeated febrile convulsions; still another had suffered a brain concussion two months prior to onset of meningoencephalitis; a 12 year old child had been diagnosed as having a brain tumor one year previously; and the fifth patient, aged 5 years, had had a right hemiplegia and suffered grand mal seizures since the age of 8 months. Two children, in addition, were considered to have had mumps one year prior to the onset of meningoencephalitis. At that time, serologic tests were not done so that a definite statement concerning recurrent mumps cannot be made.

Of the 85 patients included in this study, adequate clinical data were available in 74 cases. In 62.8% of these the signs and symptoms were predominantly meningeal; in 15.7% encephalitic, and mixed in the remaining 21.5%. Vomiting, headache and feverishness were the cardinal symptoms in the majority of cases. Drowsiness, stiffness of the

TABLE 1

TYPE OF SALIVARY GLAND INVOLVEMENT AND TIME OF OCCURRENCE IN RELATION TO MENINGOENCEPHALITIS

	None	Parotid	Submaxillary or Sublingual
Total no. of cases	38	32	11
Before encepahlitis	—	23	2
During encephalitis	—	3	8
After encephalitis	—	6	1

neck, abdominal pain and irritability were common complaints. Less frequently, backache, pain in the legs and photophobia were listed as complaints. In single instances, sore throat, cough, diarrhea, disturbance in swallowing, incoordinated eye movements, or dimness of vision were among the first symptoms noted.

Physical examination revealed fever, nuchal rigidity and positive Kernig's and Brudzinski's signs in a large number of patients. Convulsions and abnormal tendon reflexes were not uncommon findings. Pharyngeal hyperemia occurred in 13.5% of the 74 cases. Other signs of neurologic involvement were observed in isolated patients, such as nystagmus, tremors, strabismus, difficulty in swallowing, ataxia and delirium. Muscle weakness, elevated blood pressure, edema of the optic discs and abdominal tenderness were rare findings.

Information regarding involvement of the salivary glands was obtainable in 81 of the 85 cases in this series. Thirty-eight of this group of 81 patients had no salivary gland involvement, whereas 32 showed evidence of parotitis and 11 of submaxillary or sublingual adenitis. The majority of patients who developed parotitis did so before the onset of meningoencephalitis. However, in the majority of patients who developed submaxillary or sublingual adenitis, the swelling appeared during the course of meningoencephalitis (table 1).

The illness ran its course in less than one week in 9 of 55 cases where data on duration of the illness were available, whereas in seven cases it was of more than one month's duration. Thirty-three of the cases were incapacitated for from 1 to 3 weeks. Sequelae

were rare. A definite personality change was noted in one child 3½ weeks after onset of meningoencephalitis. A second child developed a left hemiparesis and the mentally retarded child, mentioned previously, ran a stormy course and was left with a residual spasticity which was present one month after subsidence of the acute illness. An 18 month old child showed ocular muscle palsy and difficulty in swallowing after a severe initial illness. Follow-up of the cases was not satisfactory because of the scattered distribution of the patients in hospitals inside and outside the state. It is conceivable that more patients with minor residual disabilities would have been discovered in an exhaustive follow-up, as reported and reviewed by Oldfelt.[20] However, the possibility of the existence of concomitant infections which could bring about such residual disabilities must be borne in mind.

Routine Laboratory Findings:* A pleocytosis in the spinal fluid was the rule, although in four instances the spinal fluid cell count was 10 leukocytes/cmm. or less. The average white blood cell count was 561 cells/cmm. A lymphocytosis occurred in all but one case. In 80.6% of the total group of spinal fluid specimens examined, 90 to 100% of the cells were lymphocytes at some point during the illness. If only early spinal fluid specimens were considered, only 69.3% of the cases demonstrated predominance of lymphocytes to that extent.

The spinal fluid protein was elevated in all but six cases. The average protein was 52.5 mg./100 cc. Spinal fluid sugar values ranged from 27 to 98 mg./100 cc. and chloride values ranged from 610 to 800 mg. Na Cl./100 cc.

The average white blood cell count was 9.8 thousand/cmm. This figure represents neither the leukopenia characteristic of viral diseases in general nor the leukocytosis common to bacterial meningoencephalitides.

A comparison of the preceding clinical and routine laboratory data with similar data tabulated by other investigators[13, 18] is presented in tables 2A and B.

Specific Diagnosis of Mumps: As pointed out in the introduction, the most rapid specific diagnosis of infections with mumps virus may be obtained on serologic grounds with the complement fixation test by a differentiation between reactions with the S and V antigens. The methods of preparing these antigens and the complement fixation technic used in earlier tests have been fully described.[17] The serologic technic has been modified subsequently as to the temperature and period of primary incubation, i.e., 18 hours at 4° C. instead of one hour at 37° C., and the hemolytic system employed, i. e., instead of a 5%, a 2% suspension of sheep erythrocytes was used with the corresponding adjustments of complement and amboceptor. Otherwise, the technic has remained unchanged. The end points are based on the initial dilution of serum giving a 3+ or 4+ fixation of complement.

Since the development of this test several years ago, it became apparent that the preparation of satisfactory S antigens is not always successful and that some of the batches could not be used. The reasons for this variability are not clear. If this fact is not taken into account, erroneous results will be obtained. In two recent publications[21, 22] an "S" antigen was employed which had been prepared in a commercial laboratory by alcohol precipitation from suspensions of infected allantoic membranes. This antigen used in conjunction with virus preparations failed to confirm the advantageousness of the S-V

* Tests performed in the various hospitals where the patients included in the study were treated.

TABLE 2A

COMPARATIVE DATA ON BLOOD AND SPINAL FLUID STUDIES

	Kilham (25 cases)	Kane and Enders (33 cases)	Present Study (51 to 66 cases)*
WBC in blood (thousands/cmm.)			
average		8.1	9.87
minimum		3.3	3.95
maximum		13.0	21.4
WBC in CSF (cells/cmm.)			
average	864	419.5	561
minimum	10	7	2
maximum	2920	1350	2890
% lymphocytes in CSF cells			
average	97.45	94.75	90 to 100 in 69.3% cases
minimum	90	70	25
maximum	100	100	100
Total protein in CSF (mg./100 cc.)			
average	56.6	—	52.5
minimum	16.6		7.0
maximum	253.0		260.0

* Above laboratory data not available for each of the 85 cases in this study. Average WBC in blood based on 55 patients, average WBC in CSF on 66 patients, average % lymphocytes in CSF on 62 patients, average protein in CSF on 51 patients.

system in the early diagnosis. A sample of this "S" preparation, when compared with the crude S preparations used in this laboratory, revealed marked differences in reactivity as shown in table 3. Although it was apparent that in 5 of the 10 cases both S antigens be-

TABLE 2B

COMPARATIVE CLINICAL DATA
(FIGURES STATED AS PERCENTAGE OF TOTAL GROUP)

	Kane and Enders (33 cases)	Present Study (74 cases)
Headache	72.5	47.3
Vomiting	64.0	67.5
Nuchal rigidity	81.5	43.3
Positive Kernig sign	25.0	28.4
Positive Babinski sign	6.0	10.8
Lethargy	25.0	28.3
Convulsions	12.5	13.5
Abdominal pain	27.5	14.8

haved differently from the V antigen, all used in optimal dilution,* it became evident also that part of the antigen responsible for the early reactions apparently had been lost or destroyed in the process of purification by alcohol precipitation. This result implies that the allantoic membranes contain more than one specific soluble component, derived from infection with the mumps virus.

As mentioned previously,[17] the appearance of antibodies to the S antigen does not always precede that of anti-V. Therefore, the S > V pattern cannot be demonstrated in all cases and the diagnosis must be based on the comparison of acute and convalescent sera. Sometimes the first serum specimen is obtained at a time when both antibodies have

TABLE 3

COMPARISON BETWEEN SOLUBLE ANTIGENS IN 5 CASES OF MUMPS MENINGOENCEPHALITIS AND 5 CASES OF MUMPS WITH SALIVARY GLAND INVOLVEMENT OR ORCHITIS

Case No.	Signs	Serum Taken Days After Onset	Alcohol ppt.	Standard	
				S	V
264	Meningoencephalitis	5	1:16	1:32	<1:2
256	Meningoencephalitis	12	<1:2	1:128	1:16
260	Meningoencephalitis	4	<1:2	1:64	<1:2
266	Meningoencephalitis	9	<1:2	1:128	n.d.
J.D.	Meningoencephalitis	28	1:16	1:64	1:256
51	Parotitis	21	1:32	1:64	1:32
243	Recurrent parotitis	?	1:4	1:4	1:64
R.O.	Parotitis and orchitis	16	1:16	1:64	1:16
F.C.	Parotitis	2	1:4	1:8	<1:2
261	Submaxillary adenitis	2	<1:2	1:8	<1:2

reached appreciable levels. In such instances, the laboratory can demonstrate evidence of recent infection, but can give no irrefutable proof that the illness under study was caused by the mumps virus. In the light of these considerations, one can divide the diagnostic results obtained in the group of 85 patients into three categories with two subgroups, as shown in table 4. A representative example of the serologic results encountered in each class is also given.

It can be seen that the S > V pattern (Category I), permitting an early presumptive diagnosis of mumps, was obtained in about one half or 43 of the cases. In 37 of these, a second serum was received which confirmed the results of the presumptive test without fail.† In six of the cases no second serum was submitted. In 19 patients both antibodies were either absent in the first serum, or present in similar concentrations or, in a few, anti-V even exceeded to some extent anti-S. Thus, the diagnosis depended on the demon-

* In many of the tests, 2-way titrations were performed; that is, varying dilutions of serum were tested against varying dilutions of antigen. In no instance did the tests reveal a better agreement between the 2 different S preparations.

† In very few instances not included in this study, a presumptive test could not be confirmed. The results were therefore considered negative for mumps. These cases consisted of a patient with parotitis and orchitis and a patient who developed a neuromuscular involvement of one eye after exposure to a case of mumps.

stration of subsequent rises in antibodies (Category II). Finally, in 23 patients the first serum revealed high titers against both antigens (Category III). Clinical information was available in 18 of these cases. In six of these, further sera were received which revealed no increment in antibodies; in the other 17, no additional sera were submitted. These patients must be considered suggestive cases of mumps meningoencephalitis, inasmuch as they had antibody titers sufficiently high to be compatible with recent mumps infection. In most instances the titers were 1:128 or higher. The lowest titer considered significant of recent infection was 1:32.

The data were analyzed further with a view to correlating the serologic categories with the occurrence of salivary gland involvement, if any, and the time of collection of the first

TABLE 4

BASIS FOR SEROLOGIC DIAGNOSIS

Category		No. of Cases		Case No.	Example			
					Serum #1		Serum #2	
					Anti-S Titer	Anti-V Titer	Anti-S Titer	Anti-V Titer
I anti-S>anti-V pattern	With subsequent rise in antibody titer	37	43	652	1:16	<1:2	1:64	1:128
(I) anti-S>anti-V pattern	No 2nd specimen available	6		201	1:16	<1:2	—	—
II anti-S = or < anti-V	With subsequent rise in antibody titer	19		87	1:4	1:4	1:16	1:128
III anti-S and anti-V high	2nd specimen obtained	6	23	539	1:128	1:256	1:128	1:128
(III) anti-S and anti-V high	No 2nd specimen available	17		2491	1:128	1:128 or higher	—	—

serum in relation to the onset of meningoencephalitis. Only 71 cases could be included in this analysis, since in the remaining 14 the available records were incomplete. The results are tabulated in table 5. In 31 out of 35 cases giving a presumptive diagnostic test in the first serum (Category I), the specimen was obtained within one week after onset of meningoencephalitis. In only seven of these (20%), was this illness preceded by salivary gland involvement; in the others, such involvement developed simultaneously with (five cases), or subsequent to meningoencephalitis (four patients), or not at all (15 individuals). This type of reaction (anti-S > anti-V) was found in only 4 of the 17 patients who were bled later than one week after onset of meningoencephalitis. In none of these four cases was meningoencephalitis preceded by involvement of the salivary glands. Thus, it is apparent that the Category I type of response is elicited early in the illness and particularly from those patients in whom meningoencephalitis is not preceded by salivary gland involvement.

In Category II, the 18 cases yielding low antibody levels against both the V and S antigens in the first serum (with anti-V = or > anti-S) and significant increases in subsequent specimens, 12 were studied within one week after onset of the central nervous system involvement and, again, only relatively few revealed preceding swelling of the salivary glands. The cases included in this group may be taken to represent failures of the rapid diagnostic test or, in other words, the early diagnosis by the anti-S > anti-V pattern appears possible in only about two thirds of the combined cases included in Categories I and II.

In Category III, composed of sera with high anti-S and anti-V titers in the first specimens, 11 of the 18 specimens were examined during the first week after onset of meningo-

TABLE 5

CORRELATION OF TYPE OF SEROLOGIC RESPONSE WITH (a) INTERVAL ELAPSING BETWEEN ONSET OF MENINGOENCEPHALITIS AND COLLECTION OF FIRST SERUM SPECIMEN AND (b) TIME OF OCCURRENCE OF SALIVARY GLAND INVOLVEMENT

Diagnostic Category	Total No.	Reports Complete	Interval Between 1st Serum and Onset of Mumps Encephalitis	Occurrence of Salivary Gland Involvement in Relation to Meningoencephalitis			
				Before	Simultaneously	After	None
I	43	35	1 wk. or less	7	5	4	15
			>1 wk.	0	0	1	3
II	19	18	1 wk. or less	1	0	3	8
			>1 wk.	2	1	0	3
III	23	18	1 wk. or less	7	2	0	2
			>1 wk.	2	2	0	3
Total	85	71		19	10	8	34

encephalitis. Seven of these were preceded by salivary gland involvement, a much larger proportion than was encountered in Categories I and II. Thus it would seem that this type of result is most likely to be found when meningoencephalitis is preceded by involvement of the salivary glands. The preceding parotitis initiates antibody formation and by the time meningoencephalitic signs have appeared, the antibody levels are already high. As regards the seven patients from whom the first serum was taken later than one week after onset of illness, the meningoencephalitis per se may have existed long enough to have given rise to relatively high anti-S and anti-V levels.

DISCUSSION

In this series of patients with mumps meningoencephalitis, the cases with and those without salivary gland involvement were about equal in number. This distribution agrees with that noted by Kane and Enders[18] and by Kilham.[13] As a rule, meningoencephalitis succeeding or developing simultaneously with salivary gland involvement offers no great difficulties in diagnosis. On the other hand, when meningoencephalitis precedes or is unaccompanied by swelling of the salivary glands, the situation is different, at least for

the first few days of illness. When the signs of central nervous system involvement are the first to appear, no clue is afforded as to their etiology unless a history of exposure to mumps within the incubation period can be elicited. Of the 45 patients in this series who never developed signs of salivary gland involvement or did so after onset of meningoencephalitis, only 12 were known to have been exposed to mumps. The remaining 33 patients posed a diagnostic problem to be solved by the laboratory. Provisional diagnoses entertained in these patients included: lymphocytic choriomeningitis, nonparalytic poliomyelitis, tuberculous meningitis, lead poisoning and toxoplasmosis. Other possibilities to be considered in the differential diagnosis are:

1. Meningoencephalitis caused by other viruses, such as herpes simplex, lymphopathia venereum, Western and Eastern equine encephalomyelitis, St. Louis (Japanese B and Russian) encephalitis, Coxsackie disease and infectious mononucleosis.
2. Meningoencephalitis caused by spirochetes, such as Weil's disease or central nervous system syphilis.
3. Irritative meningoencephalitis caused by brain tumors or abscesses.
4. Multiple sclerosis.
5. Guillain-Barré syndrome.

Of the diseases to be considered in the differential diagnosis, this laboratory has had first hand experience with the diagnostic tests for lymphocytic choriomeningitis, Eastern and Western equine encephalomyelitis, St. Louis encephalitis and lymphopathia venereum. During the period of this study, when 85 cases of mumps meningoencephalitis were diagnosed, only 18 patients with lymphocytic choriomeningitis were detected and no cases of meningoencephalitis caused by the other viruses. Thus, if one includes the cases with salivary gland involvement, the incidence of mumps meningoencephalitis is about 4½ times that of lymphocytic choriomeningitis, the second most commonly diagnosed cause of viral meningoencephalitis. The age groups involved in these two diseases appear to be quite different. Whereas more than 80% of the mumps cases were under 9 years of age, lymphocytic choriomeningitis tended to occur more frequently past the thirteenth year of life.

As to the specific laboratory diagnosis of mumps meningoencephalitis, the value of the complement fixation test differentiating between antibodies to the S and V antigens appears to be well established. An early presumptive diagnosis based on the anti-S > anti-V pattern could be rendered in some of the cases on the first or second day after admission of the patient to the hospital. However, it is not regularly possible to do so for several reasons: A. Antibodies to the V antigen may rise simultaneously with, or even precede those reacting with the S preparation. B. Sera may be submitted too late after the onset of illness, when both antibodies have already reached high levels. C. Inapparent infection of the salivary glands or other organs, like overt signs of such involvement, may precede the meningoencephalitis, and thus may have caused the appearance of high antibody levels by the time the central nervous system is affected. This possible course of events was confirmed by the demonstration of high antibody levels to S and V at the onset of primary orchitis in an experimentally exposed case. Though no salivary gland involvement had been noted, the patient excreted virus in saliva 10 and 11 days prior to onset of orchitis.[11] Similarly, it was shown by Kilham[13] that virus could be isolated from the saliva in patients with meningoencephalitis without any signs of salivary gland involvement.

Although these considerations imply that the early diagnosis cannot be attained in all

cases of mumps meningoencephalitis, they nevertheless indicate that the success of this test can be improved by submitting specimens for study as soon as meningoencephalitis is suspected, and by repeating this test at short intervals, should the first one be inconclusive. Such a close check may be difficult if the hospital where the patient is treated is a great distance from the laboratory. On the other hand, in an emergency, results of the test may become available by phone or wire within 3 to 6 hours after receipt of the serum, if the short primary incubation period (one hour at 37° C) is employed in the test. Such speed in reporting is of considerable advantage to the patient in that it may preclude unnecessary therapeutic or diagnostic procedures which are essential for other diseases considered in the differential diagnosis. Since the outlook in this disease is usually good, a positive serologic report will permit a favorable early prognosis and alleviate apprehension in parents and attending physicians.

Summary

An analysis has been presented of the results obtained in complement fixation tests employing both the soluble, or S, and virus, or V, antigens in 85 cases of mumps meningoencephalitis. Thirty-eight of 71 cases for which clinical data were complete had failed to reveal preceding, concurrent or subsequent involvement of the salivary glands. Only 25 (35%) had such involvement prior to onset of meningitis.

In 62 of the patients, definite serologic evidence of infection with mumps virus was obtained in one of two ways: (1) The presumptive test was positive in 43 cases, i.e., the first serum showed a high antibody level against the S antigen and distinctly lower titers against V. (2) In 19, a positive diagnosis was based on the demonstration of a rise in both antibodies. The remaining 23 patients gave evidence suggestive of mumps infection by virtue of high antibody levels in the first available serum.

The anti-S > anti-V pattern occurs most frequently when the meningoencephalitis is not preceded by salivary gland involvement and when the serum is obtained before the end of the first week of illness. Delay in withdrawing the blood and occurrence of overt or possibly inapparent glandular involvement prior to the meningitis is associated with the presence of antibodies in relatively high titer to both the S and V antigens. Such results can only be regarded as suggestive of recent infection.

Even when serum from patients with no salivary gland involvement is obtained in the first week of illness, about one third will not show the anti-S > anti-V pattern. At present, under proper conditions, the early serologic diagnosis appears possible in about two thirds of cases of mumps meningoencephalitis without preceding or concurrent salivary gland involvement.

The clinical findings and routine laboratory data on spinal fluids and blood are presented; these findings and data are in accord with those previously reported by others.

Acknowledgment

The authors wish to acknowledge their indebtedness to the medical staffs and laboratories of the following hospitals for making available to them the case histories and routine laboratory data used in preparing this paper: the Hospital of the University of Pennsylvania; the Philadelphia General Hospital; the Philadelphia Hospital for Contagious Diseases; the Jewish Hospital of Philadelphia; several suburban Philadelphia and out-of-town hospitals.

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Spanish Abstract

El Diagnóstico de la Meningo-encefalitis de las Paperas con Referencia Especial a el Uso de la Prueba de Fijación del Complemento

Los autores analizaron 85 casos de meningo-encefalitis desde el punto de vista clinico y serologico, con interes particular en los resultados obtenidos con la prueba de fijación de complemento. Datos clinicos fueron completos en 71 casos. De estos, 38 pacientes no demonstraron signos evidentes de parotitis a excepción de la meningo-encefalitis. Esta ocurrencia frecuente de meningo-encefalitis como

única manifestación clinica de la infección con el virus de las paperas, hace necesario el contar con una prueba de laboratorio rapida y especifica para el diagnostico de las paperas. Con este proposito, los autores hacen una evaluación de la prueba de fijación del complemento empleando los antigenos solubles y virales de las paperas.

Del grupo total de 85 pacientes, 62 de estos demostraron evidencia serologica definitiva de infección con el virus de las paperas. La muestra inicial de suero en 43 de estos casos contenía una concentración mayor de anticuerpos contra el antigeno soluble, que contra el antigeno viral, (anti-S>anti-V); ó sea una repuesta serologica de anticuerpos tipica de la infección temprana de las paperas. En los 19 casos restantes, el diagnóstico positivo fué basado en la demonstración de un aumento de las concentraciones del suero de ambos anticuerpos.

Veinte y tres pacientes en el grupo total de 85, presentaron evidencia serologica sugestiva de parotitis en los valores altos iniciales de anticuerpos. En este grupo, un gran numero de los pacientes sufrieron de paperas antes o conjuntamente con la meningo-encefalitis.

La repuesta de anticuerpos "anti-S>anti-V" ocurrió mas frecuentemente en aquellos casos en los cuales la meningo-encefalitis no estuvo precedida por una parotitis y el suero fué obtenido al final de la primera semana de la enfermedad. Los autores estiman, que con una tecnica apropiada el diagnóstico serologico de la meningo-encefalitis causada por el virus de las paperas, puede hacerse en aproximadamente dos terceras partes de los casos a pesar de la ausencia de signos clinicos de parotitis.

Finalmente se indica, que los sintomas clinicos y los resultados de laboratorio en el liquido cefalo-raquideo y sangre observados en estos casos, fueron similares a los reportados previamente por otros investigadores.

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IDIOPATHIC APLASTIC ANEMIA IN CHILDREN

Its Early Differentiation from Aleukemic Leukemia by Bone Marrow Aspiration

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IN CHILDREN one may encounter considerable difficulty in distinguishing idiopathic aplastic anemia from aleukemic lymphatic leukemia.[1-5] The clinical signs and peripheral blood pictures are so nearly identical that the differentiation may be impossible. Surgical biopsy of a lymph node or of the bone marrow is often recommended to establish the correct diagnosis.

The purpose of this report is to illustrate that, in the differentiation of the two diseases, aspiration biopsy of the bone marrow yields decisive quantitative data and a well-defined microscopic pattern, provided the volumetric and concentration technic to be described is employed.

METHODS AND MATERIALS

Clinical Materials: Four patients were admitted to Los Angeles Childrens Hospital from August 1949, through October 1950, with provisional diagnoses of aleukemic lymphatic leukemia, but subsequently they were shown to have aplastic anemia. These patients are contrasted with 9 cases of lymphatic leukemia of the aleukemic, subleukemic and leukemic varieties. This latter material represents a cross section of the cases of leukemia studied by the bone marrow aspiration method to be described.

Method: The puncture is performed in the usual manner but 2 to 5 cc. of fluid are aspirated and heparinized. Then 1 cc. of the fluid is separated into 4 layers by centrifugation in a Wintrobe hematocrit tube. The uppermost layer consists of fat; the next is plasma. Beneath the plasma is a whitish layer of myeloid and erythroid cells; these represent the nucleated cells derived from the bone marrow (termed the ME layer*). At the bottom of the tube is a column of packed red cells. The volume per cent occupied by these various layers is recorded as the volumetric data. Total nucleated cell counts are not performed; the quantity of the myeloid-erythroid layer conveys essentially the same information.

Smears for microscopic study are made from the myeloid-erythroid layer. In Cases 1, 2, 3, 4 and 7, where no myeloid-erythroid layer was present, material sufficient to make only 1 or 2 slides was aspirated from the top of the column of red cells.

The remaining 1 to 4 cc. of aspirated heparinized fluid is fixed with 10% formaldehyde in physiologic saline. Numerous particles of bone marrow tissue, as large as 1 mm. in diameter, can then be separated. If obtained, these particles are prepared for sectioning and microscopic examination thus revealing the histologic nature of the bone marrow.

The precise technics and sites employed for the bone marrow aspiration and the method of volumetric and microscopic study are described elsewhere in detail.[6]

CRITERIA

The various cells and stages of differentiation of the leukocytic series are defined according to the criteria proposed by the Committee for Clarification of the Nomenclature of

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* The abbreviation "ME" will be used in this paper to designate the myeloid erythroid layer.

Cells of the . . . Blood. . . .[7,8] The cells of the erythrocytic series are defined and classified according to the terminology of Wintrobe.[9]

An additional group of cells which apparently are closely related to, or are, lymphocytes is also mentioned. This is done for the sake of clarity and to promote accuracy. These are called in this laboratory pathologic lymphocytes and they are encountered exclusively in instances of childhood lymphatic leukemia. They are most characteristic of sub- and aleukemic lymphatic leukemia, which is more frequently seen in the 2 to 7 year age group.

On casual inspection these cells do not appear to differ from the usual lymphocyte; however, careful inspection reveals several differences which are quantitative. The most striking of these is the relative lack of cytoplasm in the presence of a large light-staining nucleus (see Fig. 1B). In the bone marrow the nuclear chromatin is never as dark or as blocked as that of the normal bone marrow lymphocyte (see Fig. 1A). On the other hand, the chromatin does not have the fine structure of the lymphoblast. The chromatin is relatively smooth or occasionally "stringy" and nucleoli are rarely visible. The nuclei often obtain a slightly lobular pattern. These cells are well illustrated in the Sandoz atlas of hematology.[10]

The larger cells of this series with light-staining nuclei are designated in this report as early pathologic lymphocytes; the smaller ones with darker-staining nuclei are called late pathologic lymphocytes. In a high proportion of aleukemic lymphatic leukemias which later become subleukemic, and in the subleukemic cases, diagnosis from peripheral blood studies is considered possible in this laboratory only when these pathologic lymphocytes reach a constant and significant (10%) number. It has not been the author's impression that, in the strict sense, "blast cells" are found in the peripheral blood of the sub- and aleukemic patient. Likewise, they are rarely seen in the bone marrow of these patients.

Tissue mast cells referred to in this report have been described and illustrated by Michels.[11]

The terms "blast cells," "leukocytic," "subleukemic," "aleukemia" and "leukemia" are employed according to the definitions of the Committee for Clarification of the Nomenclature of Cells of the . . . Blood. . . .[7,8] In order to distinguish aplastic anemia from congenital hypoplastic anemia, these terms are used in conformity with the definitions given them by Blackfan and Diamond.[12]

In this laboratory the opportunity of employing the volumetric technic in the study of aplastic anemias associated with normal or hyperplastic marrows has not presented itself. The term "aplastic anemia" as used in this report is restricted, therefore, to those cases associated with an "aplastic marrow" as described in Rhoads and Miller's group #1.[13]

The final diagnosis of aplastic anemia in Cases 1 and 4 is based on the absence of postmortem findings characteristic of leukemia.* The other two patients (Cases 2 and 3) have had only symptomatic care, including frequent transfusions, but remain alive and relatively well without significant changes in their physical, peripheral blood or bone marrow findings. The four cases (5 through 8) listed as aleukemic have either died with typical postmortem findings of leukemia or at a later date have shown peripheral blood pictures typical of leukemia. Three of these patients were treated with and responded to aminopterin and/or cortisone.

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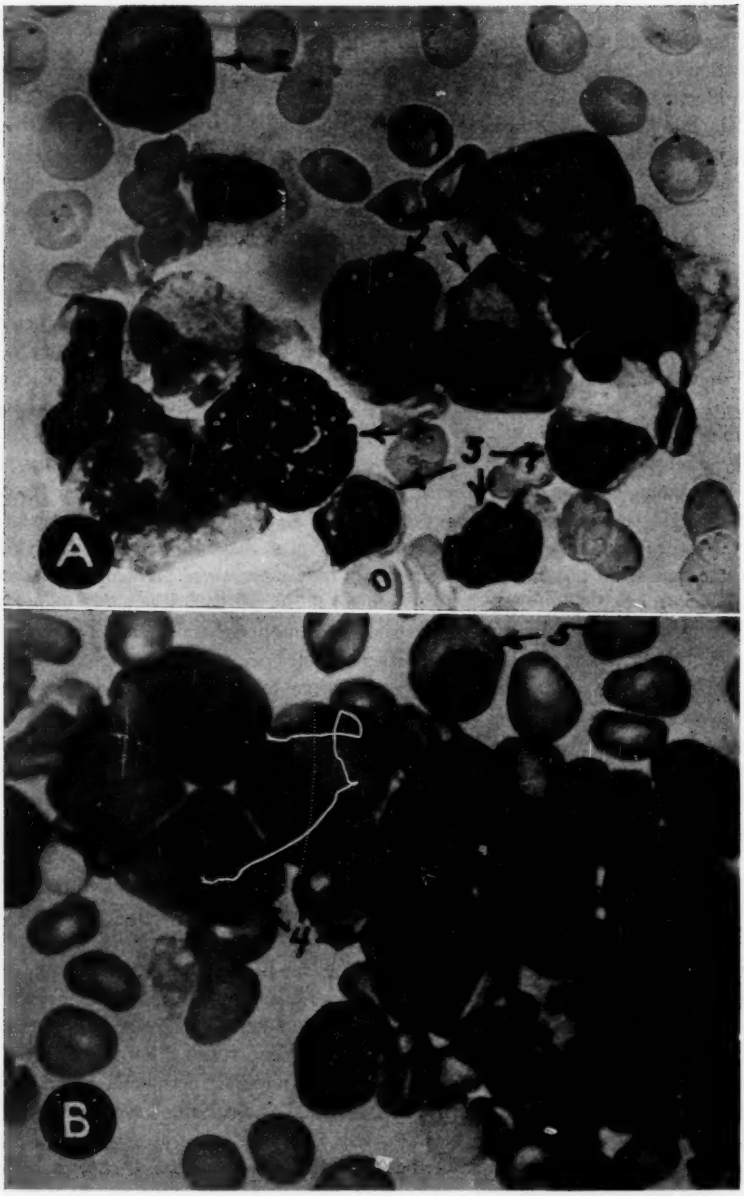

FIG. 1. Aspirated and concentrated bone marrow (× 1000). A. Case 1, idiopathic aplastic anemia showing (1) tissue mast cell, (2) plasma cells and (3) normal lymphocytes. B. Case 5, aleukemic lymphatic leukemia showing (4) early pathologic lymphocytes and (5) rare normoblast.

Observations

Clinical and Peripheral Blood Observations: Data briefly summarizing the history, physical findings and peripheral blood observations are given in table 1. The marked similarity of all these data from Cases 1 through 8 is apparent, and the consequent difficulty in distinguishing aplastic anemias (Cases 1 through 4) from aleukemic leukemia (Cases 5 through 8) is readily recognized. On the other hand, patients with subleukemic and leukemic leukemia (Cases 9 through 13) show clinical findings compatible with leukemia and on first observation had peripheral blood pictures which were diagnostic because pathologic lymphocytes were present.

Bone Marrow Observations: The previous chart illustrated a gradual transition of the clinical and peripheral blood data which made final diagnosis possible only in the cases of subleukemic and leukemic leukemias. That data failed in children to distinguish aplastic anemias from aleukemic leukemia. However, it has been noted that aspirated bone marrow, studied by concentration and volumetric methods, gives data which makes a clearcut distinction between the two diseases.

Table 2 summarizes the technical and volumetric observations from all the above material. In the four cases of aplastic anemia, the absent ME, the increased amount and rate of aspiration, and most conspicuously the increased amount of fat produce a volumetric picture diametrically opposed to that seen in all the leukemias. Although there is an occasional exception—that is aspiration is recorded as + + + in Case 11 and an occasional case of aleukemic leukemia yields no ME (as seen in Case 7)—the absence of fat in leukemias and its normal or increased amount in the aplastic anemias remain most reliable criteria.* Eleven repeat aspirations from Cases 2 and 3 have given an average fat of 3.5 mm. with a range of 1.5 to 5.0 mm.

Table 3 contrasts the bone marrow cytologic data from the four cases of aplastic anemia to the five cases of aleukemic lymphatic leukemia. The microscopic pattern in these four children is essentially the same as that described by Sundberg for adult aplastic anemia.[14] Without the use of a concentration technic, however, it appears doubtful that the smears would be cellular enough to allow recognition of this pattern. The majority of cells in both diseases are lymphocytes, but pathologic lymphocytes are uniformly absent in aplastic anemias. However, because the differences between the two types of lymphocytes are relative, one would be reluctant to have the diagnosis rest solely on this factor. The abundant plasma cells in aplastic anemia are also of value in distinguishing it from leukemia; however, here again it is a more relative matter since they are present in significant numbers in a rare case of leukemia (see Case 5).† Tissue mast cells,[11] likewise, have been encountered in this laboratory almost exclusively in idiopathic acquired aplastic anemias; however, in one case of leukemia not presented in this study a few typical tissue mast cells were noted. Despite these occasional similarities it appears that, in the majority of instances in children, one can make a reliable diagnosis of idiopathic aplastic anemia in distinction to aleukemic leukemia from microscopic study of properly prepared aspirated

* Approximately 35 cases of lymphatic leukemia have been studied by this technic; in no instance has a normal or an increased amount of fat been noted, and only on rare occasions in early cases has a trace of fat been present.

† A follow-up bone marrow in Case 5 performed 1 mo. later revealed 21% pathologic lymphocytes. At that time, although the child was clinically well, the diagnosis of leukemia was made.

TABLE 1

SUMMARY OF CLINICAL AND PERIPHERAL BLOOD DATA FROM 4 CASES OF IDIOPATHIC APLASTIC ANEMIA (CASES 1 THROUGH 4) AND 9 CASES OF LYMPHATIC LEUKEMIA (CASES 5 THROUGH 13)

Case No.	Age Yr.	Symptoms			Physical Signs			Peripheral Blood*					
		General	Hemorrhagic	Anemia	Lymph-adenopathy	Hepato-megaly	Spleno-megaly	Hgb. gm./100 cc.	WBC/cmm.	Granulo-cytes %	Mononuc-lears %	Patho-logic lympho-cytes %	Platelets appear or/cmm.
1	14	Listlessness for 3 mo.	Bruising and epistaxis, 1 yr.	Pallor for 3 mo.	None	Slight	None	4.1	2,100	23	77	0	4,000
2	2	Anorexia for 4 mo.	None	Pallor for 3 mo.	Minimal	None	None	6.0	6,000	19	81	0	Markedly reduced
3	7	Fever, colds, tonsillitis for 3 mo.	Bruising for 3 mo.	None	Minimal	Slight	None	7.7	1,600	10	90	0	5,000
4	5	Tonsillitis for 1 yr.	Bruising for 3 mo.	Pallor for 1 mo.	Slight	None	None	5.5	3,300	5	95	0	Markedly reduced
5	4	Fever for 3 mo.	None	Slight pallor, 3 mo.	None	None	None	9.0	2,000	44	56	0	Normal
6	7	Listlessness for 2 mo.	None	Slight pallor, 2 mo.	None	None	None	9.1	4,300	11	89	0	Slightly reduced
7	2	Fever for 3 wk.	None	Pallor for 3 mo.	None	Moderate	Slight	3.0	2,700	8	92	0	Slightly reduced
8	2	High fever for 7 wk.	None	Pallor for 3 wk.	Moderate	Moderate	Slight	7.4	500	16	84	0	Markedly reduced
9	2½	None	Bruising for 1 mo.	Pallor for 2 wk.	Moderate	Moderate	Marked	4.5	2,000	14	83	3	Markedly reduced
10	3½	Fever, anorexia for 1 mo.	None	Slight pallor, 1 mo.	Moderate	Slight	None	7.4	3,900	12	76	12	Slightly reduced
11	2½	Listlessness for 2 mo.	Bruising for 2 mo.	Pallor for 2 mo.	Moderate	None	None	5.1	16,500	6	41	53	34,000
12	6½	Listlessness for 2 mo.	None	Pallor for 2 mo.	Marked	Marked	Marked	5.8	24,000	2	54	44	Markedly reduced
13	½	Anorexia for 3 days	None	Pallor for 2 wk.	Marked	Marked	Marked	4.4	326,000	0	24	76	Markedly reduced

* Repeated reticulocyte counts in Cases 2 and 3 were below 1%.

bone marrow. Figure 1A is a photomicrograph of a typical field from Case 1; this is contrasted to Figure 1B, a characteristic field from Case 9.

With the technic employed in this study, the histologic nature of the bone marrow is accurately seen when particles* are obtained. However, relatively few aspirations in cases of aleukemic leukemia yield particles; but in all the cases of idiopathic aplastic anemia, particles have been obtained at least on one occasion. Figure 2A is a photomicrograph of a histologic section prepared from a bone marrow particle aspirated from Case 1. It is representative of the histology noted in all particles from the other three cases. Figure 2B illustrates the histology of a particle obtained from Case 5. The reasons for the differences in the volumetric data, previously referred to in these two diseases, is evident from their

TABLE 2

SUMMARY OF TECHNICAL AND VOLUMETRIC DATA FROM 4 CASES OF APLASTIC ANEMIA AND 9 CASES OF LEUKEMIA

Case No.	Diagnosis	Aspiration		Volumetric		Particles No. and Size
		Amount	Rate*	Fat %	ME %	
1	Aplastic anemia	6 cc.	++++	4.0	0.0	50 large
2	Aplastic anemia	3 cc.	+++	5.0	0.0	25 large
3	Aplastic anemia	3 cc.	++	4.0	0.0	50 medium
4	Aplastic anemia	4 cc.	+++	1.5	0.0	15 medium and large
5	Aleukemic leukemia	1.5 cc.	+	0.0†	1.5	0‡
6	Aleukemic leukemia	2.5 cc.	++	0.0	11.0	0
7	Aleukemic leukemia	1.0 cc.	+	0.0	0.0	0
8	Aleukemic leukemia	1.0 cc.	+	0.0	3.0	0
9	Subleukemic leukemia	1.0 cc.	+	0.0	4.5	0
10	Subleukemic leukemia	0.7 cc.	+	0.0	3.0	0
11	Subleukemic leukemia	2.0 cc.	+++	0.0	3.0	0
12	Leukemic leukemia	—	—	0.0	8.0	0
13	Leukemic leukemia	3.0 cc.	++	0.0	15.0	0

* +, 1 cc. approx. 20 sec. or more; ++, slowly; +++, average, 2–5 cc. in approx. 3–10 sec.; ++++, 5 cc. in approx. 3 sec. or less.

† Trace of fat—not enough to cover the top of the plasma layer.

‡ Particle obtained, one subsequent puncture.

respective histology. It is immediately apparent in the cases of aplastic anemia why one obtains abundant fat and no ME. On the other hand, the "tightly packed" nature of the tissue in cases of aleukemic leukemia appears responsible for the difficulty experienced in performance of the aspiration and for the absence of fat.

DISCUSSION

Differential Diagnosis: A clinical diagnosis of aplastic anemia can be made with relative accuracy when there is a history of exposure to known bone marrow toxins. However, in this clinic experiences of the last year indicate that, other than patients treated with aminopterin, aplastic anemias are of the "idiopathic" variety. Table 4 lists the agents to which the four previously presented cases were exposed within six months of the onset

* Gross effects of bone marrow tissue dislodged during the aspiration.

TABLE 3

SUMMARY OF BONE MARROW CELL DISTRIBUTION IN PER CENT FOR 4 CASES OF APLASTIC ANEMIA AND 5 CASES OF ALEUKEMIC LEUKEMIA

Cell Type %	Idiopathic Acquired Aplastic Anemia				Aleukemic Lymphatic Leukemia				
	Case No. 1	Case No. 2	Case No. 3	Case No. 4	Case No. 5	Case No. 6	Case No. 7	Case No. 8	Case No. 9
Pronormoblast	0.2	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Basophilic Polychromatophilic Orthochromatic Normoblast	20.0	10.8	2.7	2.6	28.6	0.4	4.1	0.0	6.4
Myeloblasts Progranulocytes and Early Myelocytes	2.6	1.2	0.0	0.4	0.4	0.0	0.0	0.0	0.4
Late Myelocyte Metamyelocyte Band and Segmented cells	19.0	20.2	5.5	3.6	18.4	0.6	0.7	0.2	4.1
Lymphoblasts and Prolymphocytes	1.4	1.0	0.1	0.0	0.8	0.0	0.0	1.2	1.1
Lymphocytes	45.6	57.4	82.0	89.2	48.2	12.0	3.1	13.8	6.1
Pathologic Lymphocytes	0.0	0.0	0.0	0.0	2.6	86.6	91.9	85.0	81.6
Monocytes	5.2	8.6	1.4	1.4	0.0	0.0	0.0	0.0	0.3
Plasmacytes	4.4	0.2	8.3	2.5	1.0	0.0	0.2	0.0	0.0
"Tissue Mast Cells"	1.6	0.2	less than 0.1%	0.2	0.0	0.0	0.0	0.0	0.0

of their illnesses. However, during the prodromal stage of aleukemic leukemia, therapy with the listed antibiotics, sulfonamides or antihistamines likely would be used; hence, the history of exposure to these is of little differential diagnostic value. The possible etiologic significance of some of the antibiotics and/or antihistaminics should be borne in mind. The evidence presented here, however, is only sufficient to cast suspicion on these substances; but nevertheless recent reports contain numerous references to instances of nonfatal agranulocytoses and/or anemias associated with therapeutic use of the above agents.[15–18]

Congenital hypoplastic anemia is distinguished from acquired aplastic anemia by its onset in early infancy, the absence of clinical bleeding tendencies, the presence of resistance to infections and the relatively high platelet and neutrophil count. The aplastic anemias associated with multiple congenital anomalies in the presence of the specifically

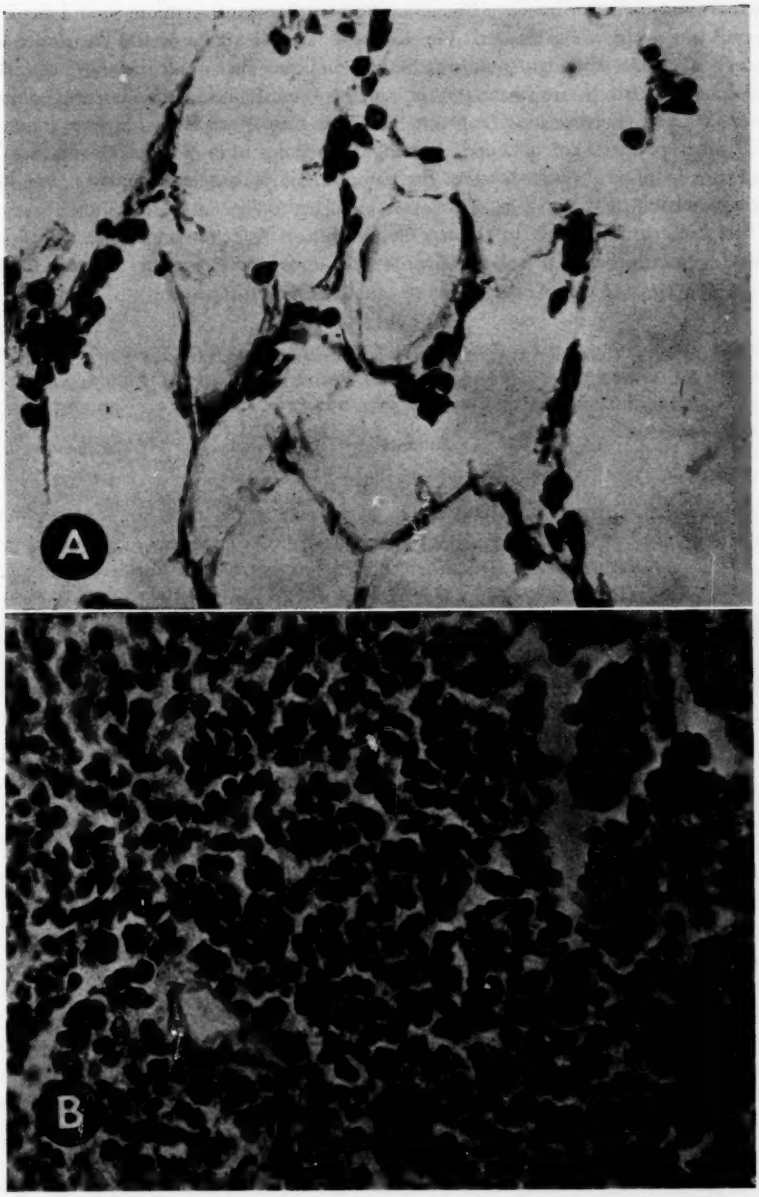

FIG. 2. Aspirated bone marrow particles (× 400). A. Case 1, idiopathic aplastic anemia showing fatty hypoplastic marrow. B. Case 5, aleukemic lymphatic leukemia showing hyperplastic marrow free of fat tissue.

associated pathology do not require further study to differentiate them from aleukemic leukemias. On the other hand, in the absence of the above information, should aleukemic leukemia be under consideration, bone marrow studies likely would be undertaken. Experience to date, although somewhat limited, indicates that in all the above conditions the volumetric patterns are essentially the same as those found in the idiopathic acquired aplastic anemias. Further long-range study of the former conditions by the volumetric (and, when particles are obtained, histologic) technics offer practical methods which may prove helpful in understanding the pathogenesis of congenital aplastic and hypoplastic anemias.

Therapeutic Implications: In children it has been of academic importance only to distinguish clinically between aplastic anemia and aleukemic lymphatic leukemia because

TABLE 4

PAST ILLNESSES, THERAPEUTIC AGENTS AND MISCELLANEOUS SUBSTANCES TO WHICH PATIENTS WITH APLASTIC ANEMIA WERE EXPOSED WITHIN 6 MONTHS OF ONSET OF THEIR ILLNESSES

Case No.	Significant Past History	Antibiotics	Sulfonamides	Antihistaminics	Miscellaneous
1	Allergy	None	None	Pyribenzamine	"Thyroid"
2	Diarrhea	Chloromycetin Penicillin Aureomycin	None	None	Phenobarbital Atropine Hyoscyamus Acetophenetidin
3	None	Penicillin	Sulfadiazine	Benadryl	Roentgenographic therapy to anterior auricular gland
4	Allergy	Penicillin Chloromycetin	Yes?	Benadryl	"Toni Wave" Turpentine Lead and zinc base paints Indelible ink

blood transfusions and antibiotics are used in both conditions. Recently, however, with newer chemotherapeutic agents, it is of considerable importance to distinguish the two diseases early in their course. Current studies in this laboratory offer suggestive evidence that aminopterin-induced remissions are longer when produced in the sub- and aleukemic leukemias rather than the leukemic leukemias. It is also noticed that the early institution of therapy in these cases is followed with fewer of the hemorrhagic complications. On the other hand, on the basis of known action of aminopterin, there appears to be ample contraindication to its use in aplastic anemias. Hence, the early diagnosis of aleukemic lymphatic leukemia and of aplastic anemia* in children and their accurate differentiation from each other has distinct therapeutic implications.

* With regard to the therapy of the latter conditions, several agents have been tried. In the 2 patients who have now survived approximately 1 yr., folic acid and vitamins B_{12}, "P," "C" and "K" have produced no observable benefits in general or symptomatically. Cortisone, ACTH and toluidine blue were tried in one of the patients who died.

Summary and Conclusions

With the use of the concentration and volumetric bone marrow aspiration technics in the differential diagnosis of idiopathic acquired aplastic anemia from aleukemic lymphatic leukemia in children, it is possible to establish an early reliable diagnosis. In this clinic specific therapy with the indicated agents has not had to await an indefinite period of observation pending the development of unmistakable clinical and peripheral blood signs nor the more difficult procedure of surgical biopsy.

Bone marrow aspirations performed in four cases of aplastic anemia and studied by these technics have shown normal or increased ease and rate of aspiration, normal or increased fat, and absent myeloid-erythroid layer.

Five cases of aleukemic leukemia presented as typical of numerous others studied revealed marked difficulty in the aspirations, absent fat and a variable myeloid-erythroid layer.

Study of histologic material obtained with the use of the preceding technics revealed the marrow from all cases of aplastic anemia to be fatty and hypoplastic in contrast to the marrow from a case of aleukemic leukemia, which was hyperplastic and without fat tissue. These later observations correlate well with the observed differences in volumetric data.

Addendum

Since completion of the above manuscript, one of the two surviving patients died from a subarachnoid hemorrhage; the other surviving patient has made a spontaneous recovery with return to normal of all hematologic abnormalities. In addition, two other patients have been studied. One died during the first few weeks of her disease. There was no known exposure to chemicals, drugs or antibiotics. Gross postmortem findings do not suggest leukemia. The other child had had repeated exposure to several organic solvents. His general condition remains satisfactory. Both cases showed volumetric, cytologic and histologic bone marrow findings identical to those described for the previous cases.

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SPANISH ABSTRACT

Anemia Aplastica Idiopática en Niños; Su Distincioń Temprana con la Leucemia Aleucemica Mediante la Punción de la Medula Ósea

El autor opina que frecuentemente hay dificultades en distinguir la anemia aplastica de la leucemia aleucemica basandose en el criterio clinico y en el exámen de la sangre periferica. El estudio de la medula ósea mediante la técnica volumetrica y de concentración realizado en cuatro casos de anemia aplastica, resultó en la obtención de datos muy útiles para el diagnóstico entre las dos enfermedades. La centrifugación del material obtenido de la medula ósea de casos de anemia aplastica en un tubo de Wintrobe (hematocrito), resultó en la ausencia de la capa mieloeritroide y en el aumento de la cantidad de grasa. En contraste, en los casos de leucemia aleucemica se observó la ausencia de grasa y la presencia a veces aumentada de la capa mieloeritroide. Otras diferencias se encuentran en la facilidad de la punción de la medula ósea y en las caracteristicas citologicas e histologicas.

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REPEATED RECOVERY OF A SPIRILLUM BY BLOOD CULTURE FROM TWO CHILDREN WITH PROLONGED AND RECURRENT FEVERS

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THE purpose of the present communication is to report the unusual clinical histories of two children who suffered from prolonged illnesses which were not unlike Sodoku. The unique feature of these cases is that a spirillum which morphologically resembled Spirillum minus was repeatedly cultured over a period of years from the blood stream of both children. Because of this unusual feature this organism will be described in some detail.

A good review of Sodoku is contained in the paper of Brown and Nunemaker.[1] In its typical form the disease is contracted from the bite of a rat though cases have been attributed to the bites of cats, dogs and other animals. The initial wound heals without signs of local inflammation. One to three weeks later the overt disease begins with the development of a chancre at the site of the bite, lymphangitis, lymphadenitis and fever. After a few days, the fever and local lesion subside only to be followed after a few afebrile days with a second bout of fever and increased signs of inflammation in the wound. A rash almost always accompanies these exacerbations. Some cases are reported to subside spontaneously and others to last for months. In about half the cases a positive serologic test for syphilis develops. Treatment with penicillin or one of the antisyphilitic arsenicals is usually dramatically and completely effective. In the past, attempts to substantiate the clinical diagnosis by demonstration of the causative micro-organism have been successful only following animal inoculation, or after dark field examination of material from the wound or a lymph node. Attempts to cultivate this organism on artificial media have failed with the exception of a case of subacute bacterial endocarditis reported by Hitzig and Liebesman[2] from this hospital.

CASE REPORTS

Case 1.—L. G., born in the United States, had a normal infancy and early childhood until 6 yr. of age when it was noted that he was febrile. The temperature was usually low-grade but occasionally went to 40.0° C. Two months later he was admitted to a hospital in Washington, D.C., where after 2 wk. of observation he was discharged without a definite diagnosis. He developed increasing weakness, abdominal distention, eructations, vomiting, anorexia and a gradual loss of 6.8 kg. in weight. The skin became dry and rough. Soon difficulty in the use of the legs appeared and walking became painful. Three months later the boy was admitted for study to The Mount Sinai Hospital in New York City.

The physical findings on admission were as follows: The patient appeared emaciated, weak and chronically ill. He weighed 25.4 kg. He walked on a wide base with real difficulty and was unable to climb onto a low chair. He heard and spoke well and was mentally alert. The skin was dry and showed an acneform, papular, hyperkeratotic eruption with numerous comedones on the face and extremities. Ears, nose and throat were normal. The tongue was reddened with

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hypertrophic papillae. There was no adenopathy. Lungs were normal and heart rate was 110 and regular. There was a faint apical systolic murmur. The heart did not appear enlarged. Blood pressure was 110/55 mm.Hg. The abdomen was tympanitic, markedly distended but not tender. The liver edge was felt 2 cm. below the costal border. The spleen could not be felt. Rectal examination revealed no abnormal findings. Except for absence of the knee jerks, neurologic examination was also normal. The ocular fundi were normal. The teeth were in extremely poor condition, blackened, decayed and worn down almost to the gums.

Laboratory data were as follows: Hgb. 11.5 gm./100 cc. (81%); WBC count 22.9 thousand/cmm.; polymorphonuclear neutrophiles 7%; nonsegmented forms 8%; lymphocytes 82% and monocytes 3%. Total blood protein 5.2 mg./100 cc. Phosphorus 4.6 mg./100 cc. Calcium 10.8 mg./100 cc. Wassermann and tuberculin tests were negative. Urine was normal. Stools were pale, guaiac negative and at times showed abnormal amounts of free fat (Sudan III). Tourniquet test was positive. Prothrombin time was normal. Gastric analysis showed achlorhydria. Gastrointestinal roentgenographic series showed an unusual delay of transit throughout the entire tract including the esophagus, suggesting a neurogenic disturbance. Chest RG showed no abnormality. Basal metabolism was −32%. A vitamin C test indicated a marked deficit. No vitamin A could be demonstrated in the blood. Glucose tolerance test was normal. A skin biopsy revealed hyperkeratosis with lymphocytic infiltration, but the histologic findings were not diagnostically significant. Biopsy of a lymph node showed simple hyperplasia.

The child continued to have low grade fever. His eating habits were poor; at times he would take 2 hr. to finish a meal. It was evident that the boy was suffering from multiple vitamin deficiencies which could account for the skin condition and the difficulty in locomotion. However, the underlying disease was not apparent until a blood culture revealed the presence of a spirillum. In view of this finding the history was reviewed and it was ascertained that immediately preceding the first signs of illness, the boy, while playing in the woods near Washington, D.C., received a laceration in the thigh from a low growing branch. The wound healed slowly and left a deep scar. It was known that there were numerous rats in the woods.

With the finding of a positive blood culture, the administration of penicillin was begun (75,000 units every 3 hr.) and 3 blood transfusions were given. The fever responded well to penicillin although the organism in vitro proved markedly resistant to the drug. Two succeeding blood cultures were positive for the spirillum, but after 2 wk. of treatment, a negative blood culture was obtained. This was followed by several negative cultures during the next 2 mo. Penicillin was continued for 3 more weeks so that the total dose was over 18 million units. Injections of liver were also administered and psychotherapy and occupational therapy were employed.

The patient was discharged from the hospital after 4 mo., at which time his skin was clear, appetite and eating habits were greatly improved, weight was 21.8 kg., gait was normal, abdomen was no longer distended, but the teeth were still in bad condition. The diagnoses on discharge were rat bite fever, with malnutrition, avitaminosis and severe conduct disorder. The child was sent to a convalescent home where he improved considerably. On his return home it was noted that he again exhibited fever and a blood culture taken 12 days later again showed the presence of the spirillum. One month later the boy was readmitted to the hospital where he was again given penicillin in doses of 200,000 u. every 3 hr. for 3 wk. without affecting the blood stream infection. Arsenic in the form of mapharsen in large doses also was found ineffective. At this time streptomycin became available and since in vitro tests showed the organism to be sensitive to it, this drug was administered in doses of 2.0 gm. daily. However, though several sterile blood cultures were obtained while streptomycin was being administered, as soon as the drug was discontinued, spirilla again appeared in the blood. After 4 mo. the patient was taken from the hospital against advice and was not admitted again until 7 mo. later. At this time, 1 yr. and 4 mo. after the discovery of spirilla in his blood, the boy still looked ill and still spent a good part of the day unsuccessfully trying to eat. Low grade fever continued.

From this admission till his death 9 mo. later, the patient's time was about equally divided between his home and the hospital. At times his general condition seemed much improved and he gained weight, at others he relapsed into his original state of malnutrition. About 3 mo. before death mental symptoms made their appearance. He became forgetful and at times quite incoherent. On his final admission to the hospital at 9 yr. of age he was unresponsive and unconscious of his surroundings. He showed fixed pupils, nuchal rigidity, nystagmus and choked discs. Lumbar tap

revealed xanthochromic fluid with 40 WBC/cmm. Pandy reaction was 4+. Culture of the fluid was sterile. WBC count was 9.5 thousand/cmm. with a shift to the left, and marked toxic granulation. Blood culture was positive for the spirillum. Electroencephalogram corroborated the neurologist's diagnosis of diffuse meningoencephalitis.

For several days the boy lay in a stupor and it was noted that the abdomen was becoming gradually more distended while complete obstipation was present. Radiography revealed enormously dilated loops of bowel suggesting obstruction. Accordingly his abdomen was opened and a volvulus of the transverse colon was found and reduced. The patient made a good postoperative recovery and for a few days the mental status seemed to be improving, but after 2 wk. it again deteriorated and the child died 6 wk. after hospitalization. No autopsy was permitted.

Summary: A 7 yr. old boy (L. G.) was admitted to The Mount Sinai Hospital with a history of unexplained fever for 18 mo. previous to which he had been in excellent health. Fever was interrupted by short remissions but was accompanied by severe anorexia, weakness, abdominal distention, vomiting and gradual loss of 6.8 kg. in weight. On admission he showed signs of multiple vitamin deficiencies, especially keratosis and multiple neuritis. A thorough work-up failed to show the underlying cause of the fever or the avitaminosis until a blood culture revealed the presence of a spirillum. It was then ascertained that the boy had sustained a deep laceration of the thigh while playing in a rat-infested woods. Dietary regulation, blood transfusions, liver injections and vitamins improved the child's nutrition but failed to affect the blood infection. In spite of intensive treatment with penicillin, streptomycin and various arsenic and bismuth compounds, blood cultures with few exceptions remained positive. The illness was terminated by encephalitis. The patient died 2½ yr. after the onset of fever and 2 yr. after the discovery of spirilla in the blood which were still present at the time of death.

Case 2.—P. F. was born at term without difficulty. He was normal and weighed 2.9 kg. He weighed 13.6 kg. at 1 yr. Episodes of running nose and cough were frequent in infancy. At 2½ yr. rubeola was followed by pneumonia and several spells of diarrhea. He improved on a celiac diet. He was taken to Florida at 3 4/12 yr. and remained there for 2 wk. During the next 15 mo. he had several febrile periods and seemed irritable, restless and had difficulty falling asleep.

At 4½ yr. of age he fell from an arm chair to a carpeted floor striking his head in the right temporal area. Evidence of injury was limited to slight amount of local swelling. Nevertheless during the next 2 mo. he became anoretic and had several episodes of projectile vomiting. He developed intermittent severe bitemporal headaches, and became progressively more lethargic. He frequently fell asleep before his customary bedtime and in odd places. Two months after the fall, he developed progressive weakness of the left arm and of the left lower extremity. An EEG made 1 mo. later revealed a high voltage, slow wave focus in the right parieto-occipital area. A pneumoencephalogram was interpreted as showing an area of atrophy in the right cerebral hemisphere. Two months later he had a left-sided convulsive seizure with fever of 41.1°C. which lasted for 2½ hr. and was controlled only by general anesthesia. For the next 2 mo. he was observed in a hospital where the diagnosis was left-sided hemiplegia of undetermined cause and generalized arteriolar disease of undetermined type.

Four months later, at 5 4/12 yr. of age, he fell on the sidewalk and struck his right forehead. A hematoma developed at the site of injury and within 1 mo., a large clear serum-containing blister has formed. For months the blister re-formed after being ruptured by a physician or by accidental trauma. Eventually a firm eschar-like lesion formed at the site which persisted.

Five months and again 7 mo. after the fall, he was hospitalized for sinusitis, pneumonia and agranulocytosis. The WBC ranged between 1.3 and 2.0 thousand/cmm. and there were only 8 to 11% polymorphonuclear leukocytes. A biopsy of an anticubital nodule revealed on microscopic section possible periarteritis nodosa or lupus indurativa. His neurologic status was unchanged.

At 6 yr. of age he was admitted to The Mount Sinai Hospital because of cough and fever for 3 days. He was poorly nourished, looked chronically ill and had evidence of atelectasis and pneumonitis of both lower lung fields, pansinusitis and purulent otitis media. On the right forehead, there was a 3 sq. cm. yellowish brown crusted lesion and on the left buttock, there were similar lesions which first appeared at sites of penicillin injections. Left hemiparesis and hemilateral hyperreflexia, positive Babinski and Hoffman signs were noted and also left facial and left-sided tongue weakness. The left foot was plantar flexed and the left achilles tendon markedly shortened. No sensory loss was noted and no cerebellar signs were elicited. Review of the pneumoencephalogram done in another

hospital did not confirm the opinion that there was cortical atrophy on the right. EEG, skull RGs and examination of the spinal fluid done at this hospital were all negative. It was felt that the hemiparesis was due to a single subcortical focus on the right involving the pyramidal and extrapyramidal systems.

Bone marrow revealed increased erythropoeisis. WBC count was 3.0 thousand/cmm. with 52% segmented forms, 26% nonsegmented forms, 19% lymphocytes and 3% monocytes. Subsequent counts ranged from 2.0 to 4.5 thousand/cmm. Many urinalyses and stool examinations were negative. Repeated blood Wassermann tests, tuberculin tests up to 1 mg., guinea pig inoculation of gastric aspirations and a coccidioidin skin test were all negative. Dark field examination and cultures of the skin lesions were negative. A lymph node biopsy showed chronic inflammation and a review of the material biopsied at another hospital failed to confirm the diagnosis of diffuse vascular disease.

For 4 mo. therapy was directed to the sinusitis and pneumonitis. Penicillin was used as an aerosol; it was instilled into the trachea and bronchi several times and for almost 8 wk. was injected intramuscularly in doses up to 250,000 u. every 3 hr. Skin tests for an allergy were negative and eosinophiles were never noted in the pulmonary or nasal secretions. From the nasopharynx, from the material suctioned through a bronchoscope and from the sinus washings, Str. viridans, Staph. albus and B. coli were recovered; from the right ear pus B. pyocyaneus.

He had intermittent febrile spikes of short duration up to 39.4°C. accompanied by moderate splenic enlargement and on several occasions by a blotchy pink facial eruption which lasted only as long as the fever.

The resemblance and similarity of the skin lesions on the forehead of the patient to the skin lesion on the forehead of a child with rat bite fever portrayed in the fourth edition of *Mitchell and Nelson's Textbook of Pediatrics* suggested the possibility that this patient was suffering from Sodoku, and so a renewed search for the etiologic agent was started. A blood culture done 4 mo. after admission yielded a spirillum minus-like organism.

The mother then recalled that, 3 yr. previously, during the Florida hurricane in October 1944, the child awakened from sleep crying in pain and a small laceration surrounded by large red area was seen on one arm. It was presumed to be a spider bite, but in retrospect it probably was a rat bite as rats were prevalent in and near the house and seemed to be disturbed by the hurricane. The mother also recalled that during several febrile periods in the next year red macular lesions appeared over both pretibial areas and turned blue-green before they faded, also that during that year her son's behavior changed.

Several blood cultures taken at intervals of a few days were positive for the same spirillum and dark field examinations of the scrapings obtained beneath the crusts of the lesion on the forehead was also positive for the spirillum. As already indicated, attempted therapy with penicillin failed. In vitro the spirillum was found susceptible to streptomycin and mapharsen. Thereafter mapharsen 0.001 gm./kg. was given intravenously every other day for 10 doses. Following this the spirillum was again recovered from the blood and consequently streptomycin 1.5 gm. daily was given for 4 wk. with only temporary clearing of the blood. Mapharsen, sulfadiazine and streptomycin were then given simultaneously, without lasting result. The spirillum had, by 1½ mo., become resistant to mapharsen 0.1 to 0.2 mg./cc. but the susceptibility to streptomycin was unchanged. Streptomycin therapy was then repeated giving 2 gm. daily. This time blood cultures continued to be positive during treatment with streptomycin even though the in vitro susceptibility of the spirillum had not changed.

A search for the organism by culture and dark field examination of the nasal and sinus washings, bronchial secretions and gall bladder drainage and skin lesions failed to locate the focus of infection. Treatment with polymyxin B was considered but the resistance of the spirillum to this drug was too great to warrant its use. Since no further therapy was contemplated at this time, he was discharged 1 yr., 2 mo. after admission.

Six days later, he was readmitted because aureomycin had become available and in vitro sensitivity of the spirillum was demonstrated. His physical condition was poor; he was emaciated and very ill. The skin lesions were unchanged. The ear and sinuses were discharging pus. The pulmonary and neurologic findings were unchanged. A blood culture was again positive for the spirillum.

The patient was given aureomycin 500 mg. 4 times daily. After 10 days the temperature was

normal, total WBC count was 3.1 thousand/cmm. with 14% nonsegmented forms. The erythrocyte sedimentation rate was 4 mm. Therapy was discontinued and blood cultures during this time showed no further growth of the spirillum. Nevertheless, because of previous experience with this patient, he was given a course of intravenous aureomycin for 4 days, receiving on the average 500 mg./day intravenously and was again given 500 mg. 4 times daily by mouth. He was maintained on this oral therapy for the duration of his hospitalization (6 wk.) during which time he was afebrile and showed a slow but gradual improvement in his general condition including a gain in weight to 23.5 kg. Blood cultures following the institution of aureomycin were consistently negative. The patient was discharged on a regime of aureomycin 2.0 gm. by mouth daily. This was at the end of 17 mo. of almost continuous hospitalization caused by an illness which probably dated back 4 yr. Since discharge the boy has had repeated negative blood cultures. He is now attending school.

Summary: A white male of 6 yr. (P.F.) was admitted to The Mount Sinai Hospital because of fever and cough. He had fever, pansinusitis, bilateral pneumonitis, right otitis media, left hemiplegia and several indolent skin ulcerations. There was leucopenia with a tendency to agranulocytosis. He had been in 5 hospitals during the previous 3 yr. because of pneumonia and his neurologic condition. Despite months of observation and treatment with sulfonamides and penicillin at this hospital, no progress was made until a Spirillum minus-like organism was recovered by blood culture. A probable rat bite 3 yr. previously was then recalled by the parents. The spirillum was found to be sensitive in vitro to mapharsen and streptomycin, but intensive therapy with either drug or both in combination yielded negative blood cultures for only 2 to 4 wk. Aureomycin finally cured this boy's disease.

Bacteriology

A spirillum was recovered in a routine blood culture from the first patient (L.G.) for the first time six months after the first signs of illness. It was subsequently recovered 15 times. A similar organism was recovered from the blood stream of the second patient (P. F.), also by routine blood culture technic, for the first time four months after admission to this hospital. It was subsequently recovered 16 times. Despite numerous attempts, the organism was never cultured from any other body fluid or tissue, but was demonstrated once on dark field examination of scraping from one of the skin lesions of P. F.

The media and technic routinely used for blood culture at The Mount Sinai Hospital have been described in a paper by Shwartzman and Goldman.[3] The media consist of nutrient broth containing PABA, glucose and yeast broth in 100 cc. amounts in flasks, a cooked liver anaerobic tube, and two glucose and one plain agar pour plates. Approximately 20 cc. of whole blood is drawn and distributed as follows: 5 cc. into each of the flasks, 2 cc. into the liver tube and into each of the plates. Some of these media are kept under reduced oxygen tension and with increased CO_2. Repeated subcultures are made at regular intervals.

The spirillum recovered from each of these children grew quite well in broth aerobically and also with added CO_2. It grew with difficulty anaerobically. On first isolation, the broth usually appeared clear, though smears revealed the organism. After repeated subcultures, a regular order of events was noted. A surface accumulation of material was observed after about three days, which after two more days often fell to the bottom of the flask as a stringy, slimy mucoid mass. Smears of this material revealed the characteristic morphology shown in Fig. 1A. The organism was subcultured usually at weekly intervals, in the first instance (L. G.) for five years and in the second instance (P. F.) for eight months. During the course of prolonged passage, it was observed that the spirillum varied in shape, often becoming rod-like (see Fig. 1B) and some months later reverting to a more typical spiral shape.

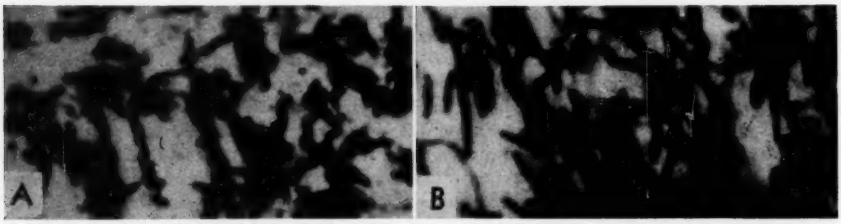

FIG. 1A. Typical appearance of cultivated organism (P. K.) 1B. Rod-like phase in cultivated organism (L. G.).

The organism grew fairly well on chocolate or blood agar plates in circular convex colonies which were smooth-edged, whitish grey and glistening. The P.F. strain differed from the L.G. in that it was mucoid. There was scant growth on plain agar and none on Endo, corn meal, Sabouraud's or GPI (Gram-Positive Isolation) agar. The usual biochemical tests were negative even though there was apparently good growth in all the media. There was no fermentation of dextrose, maltose, mannite, lactose or saccharose. The indol, nitrate reducing, urea splitting, methyl red, litmus milk and Kligler tests were all negative.

When lyophilized, the culture was viable for as long as three months.

Mice were injected intraperitoneally with both strains; no overt disease was produced and it was not possible to recover the organism from these animals after 10 to 14 days.

Appearance Under Electron Microscope: The spirillum when seen with the electron microscope was found to have typical bipolar tufts of flagella and to contain accumulations of intraprotoplasmic material, probably volutin granules (see Fig. 2).

Chemotherapy: The similarities and differences between the spirilla recovered from these patients are summarized in table 1. They were alike in that in vitro both were resistant to penicillin and sulfadiazine. They differed in that #2 (P.F.) was susceptible to streptomycin (being inhibited by 0.2 μg.), while L.G. required 10 to 100 μg. to inhibit its growth. The P.F. spirillum never became resistant to streptomycin despite the fact that the patient was treated intensively with this agent for many months. The P.F. organism was also relatively susceptible to both aureomycin and chloromycetin, requiring only 2 and 4 μg., respectively, while the L.G. was resistant to aureomycin and only slightly sus-

FIG. 2. Appearance of organism (L. G.) under electron microscope.

ceptible to chloromycetin. Both P.F. and L.G. strains were approximately equally susceptible in vitro to mapharsen. (These in vitro chemotherapeutic tests were carried out in the chemotherapeutic unit of the Department of Bacteriology under the direct supervision of Dr. Stanley S. Schneierson.)

Serology: The organisms were both antigenic since, when they were inoculated into rabbits, the animals developed high agglutinin titers. However, there was relatively little cross agglutination by the sera obtained from the two strains. For example, in a slide agglutination test using the L.G. organism and rabbit sera prepared against the L.G. and P.F. spirilla, the homologous serum was found to cause agglutination in a dilution of

TABLE 1

COMPARATIVE SENSITIVITY OF 2 SPIRILLA TO CHEMOTHERAPEUTIC AGENTS

Agent	Organism	
	#1 (L.G.)	#2 (P.F.)
	Inhibited by	
Streptomycin	10–100 μg.*	0.2 μg.
Aureomycin	>100 μg.†	2 μg.
Chloromycetin	10 μg.	4 μg.
Terramycin	1–10 μg.	ND‡
Polymyxin	100 μg.	0.08 μg.
Bacitracin	>100 μg.†	ND
Penicillin	500 u.	30 u.
Sulfadiazine	>100 mg./100 cc.†	>100 mg./100 cc.†
Mapharsen	0.05–0.5 mg./100 cc.	0.01–0.2 mg./100 cc.

* μg.—micrograms
† Not inhibited by 100 μg.
‡ Not done.

1:64 while agglutination with the heterologous serum was not obtained in a dilution beyond 1:8. Neither patient developed any significant level of agglutinin during the course of his illness.

DISCUSSION

The clinical picture presented by each of these two children when first seen by the authors was primarily that of prolonged inadequately explained fever. Yet in at least the second child (P.F.) the involvement of the central nervous system, the respiratory tract and skin suggested a chronic disease like syphilis or Sodoku. A classical clinical pattern of this disease has been outlined in the literature; nevertheless study of the reported cases makes it clear that variations from this are not uncommon. Consequently, it is not difficult to reconcile with a diagnosis of Sodoku the absence of a characteristic chancre in the first child, the failure of both children to develop a positive serologic test for syphilis or their failure to respond to treatment with penicillin and arsenicals. However, the identification of the repeatedly recovered spirilla presents a puzzling problem.

Spirillae are not too well known, although they contain a few species of considerable medical interest. They are curved gram-negative organisms which are usually highly

motile by virtue of polar flagellae. Taxonomically they are divided into at least six genera, only two of which contain organisms pathogenic for man.[4] These are Vibrio, which include the etiologic agent of cholera, and Spirillum. Most of the species of Spirillum are found in soil and water and are not pathogenic. The single species recognized as capable of producing disease in man is the Spirillum minus. This is characteristically a short cell, 1 μ or less in diameter and consisting of 2 to 3 windings, which is actively motile by virtue of bipolar tufts of flagella. The name Spirillum minus is derived from the original name Spirillum minor given by Carter in 1887 to indicate the small dimensions of the organism. (Robertson[5] in 1924 noted that Carter did not take into account the fact that the generic name Spirillum is neuter. To correct this error, Spirillum minor was changed to Spirillum minus.) Spirilla are readily differentiated from treponema by the fact that in motion the body of the spirillum remains rigid, while the treponema is flexible along the long axis. In *Bergey's Manual of Determinative Bacteriology,*[4] it is stated that unlike most other species of spirillum, Spirillum minus does not grow on artificial media, and no volutin granules are observed within the organism. Spirillum minus has been found in the blood stream of a variety of apparently normal rodents.

As noted, in 1887 Carter reported the occurrence of a minute spirillum in the blood of an Indian rat.[5] In 1916 Futaki, Takaki, Taniguchi and Osumi[6] studied two patients with rat bite fever and observed "spirochaetes" in dark field preparations from skin biopsy material. The same authors published later a paper with drawings of the organism which differed considerably from their first report.[7] However, this second description resembled more closely the spirillum described by later workers as the cause of rat bite fever. In 1921 Adachi[8] published the first photomicrograph of these organisms along with a clear description. He studied six strains, only one being from a human case. He described a short thick body (about 3 μ) with 2 or 3 windings which were thick and regular. As to the flagellae, "sometimes many slender flagella unite into one long one or one long one divides into several small ones. Some long forms have flagella arising at the middle of the body." It was Robertson in 1924[5] who concluded from his own observations and a study of the literature that the organism described as the cause of rat bite fever in man was the same spirillum which is seen in the blood of animals. Therefore, following the rule of priority, he proposed the name Spirillum minus, Carter 1887, which is now generally accepted as the name for the causative agent of Sodoku.

Many attempts have been made to cultivate this organism. Joekes[9] in 1925 claimed to have been successful in 3 out of 6 attempts to grow the spirillum from the blood of infected guinea pigs. Indeed he presumably made 34 subcultures in 1% glucose broth with added rabbit blood. However, although the cultures were always made under strict aseptic conditions, "all showed a motile coliform bacillus as well as the spirilla." It would seem that this organism had never been satisfactorily cultivated on artificial media until Hitzig and Liebesman[2] did so, from the blood of a patient with subacute bacterial endocarditis. The two patients who are the subject of this communication are the only ones with an illness resembling Sodoku from whose blood a spirillum has ever been unequivocally recovered on artificial media. In both these instances it was done, as in the case reported by Hitzig and Liebesman, during the course of a routine blood culture on standard bacteriologic media. Because of the relative ease with which the organisms reported in this paper were cultivated and maintained on artificial media, one might question whether we are dealing with a classical Spirillum minus, despite the morphologic similarity. Yet in the standard *Manual of Determinative Bacteriology,*[4] this organism is

differentiated solely on the basis of morphology and pathogenicity. On both points the organism recovered from these two patients may be classified as a Spirillum minus.

The organisms from these patients differed from each other in their growth characteristics and immunology, but even more strikingly in their varied susceptibility to chemotherapeutic agents. It is not yet clear whether these differences are merely strain variations, or are indications for division into two separate sub-types. Similarly, as already referred to, the present investigators do not yet know whether the very fact that both these organisms were readily cultivated on artificial media, and that both were insensitive to penicillin, should be considered sufficient for their classification as an entirely new pathogenic species of Spirillum or merely as variants of the classical Spirillum minus. Dodd[10] has observed some patients with Sodoku which required for cure six months or more of arsenical therapy. The eventual answer to both these problems awaits further study of clinical material. Meanwhile, because of the clinical course of these two patients and the unusual bacteriology, it may perhaps be more accurate to set this syndrome apart from classical Sodoku or rat bite fever and use the simple descriptive term "Spirillum Fever," or "Spirillary Fever" as recently suggested by Watkins.[11]

Summary

A spirillum was repeatedly recovered by blood culture from two children. This organism resembled the Spirillum minus which has long been associated with one form of rat bite fever, Sodoku. In Sodoku the spirillum is usually recovered by animal inoculation and no previous record has been found in which a diagnosis has been made by blood culture.

The organisms recovered from the two patients were morphologically indistinguishable from the classical Spirillum minus, but were unique in that they could be maintained for many months on standard liquid and solid bacteriologic media. Their in vivo resistance to penicillin and arsenicals was marked and therefore also unusual.

Both patients were seen because of recurrent fever, eruption and symptoms referable to the central nervous system, respiratory and intestinal tracts. The first child was admitted to The Mount Sinai Hospital debilitated and febrile. A spirillum was recovered repeatedly on routine blood culture, although there was no definite history of rat bite. Treatment with arsenicals and penicillin and streptomycin failed and the patient died. The second child was admitted with a history of repeated respiratory infections and indolent skin ulcers and hemiplegia. He had apparently been bitten by a rat while in Florida 3½ years before the spirillum was first recovered from his blood. Treatment with penicillin and sulfarsphenamine was ineffectual. The organism was sensitive in vitro to streptomycin but as much as 2 gm. a day for several months failed to do more than induce several negative blood cultures. Treatment with aureomycin finally succeeded in sterilizing the blood stream and healing the ulcers. Coincident with this there was a striking improvement in the child's general condition.

The clinical course of these two patients and the unusual bacteriologic findings set them apart from classical rat bite fever and suggest use of the term "Spirillum Fever."

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SPANISH ABSTRACT

Hemocultivos Positivos de Spirilum Obtenidos en Dos Niños con Fiebre Recurrente Prolongada

Hemocultivos positivos de Spirilum fueron repetidamente obtenidos en dos niños. Este organismo se parecía al Spirilum minus él cual es el agente etiologico del Sodoku. En los casos de Sodoku, el Spirilum es generalmente identificado mediante la inoculación a animales, pero su aislamiento mediante cultivos de sangre no había aún sido reportado.

Los organismos aislados en estos dos pacientes fueron morfologicamente indistinguibles del clásico Spirilum minus, pero con la particularidad de que pudieron ser mantenidos viables por varios meses en medios bacteriologicos liquidos y sólidos. La resistencia "in vivo" a la penicilina y a los arsenicos fué marcada y por consiguiente infrecuente.

Ambos pacientes sufrieron de fiebre recurrente, erupciones y sintomas referibles al sistema nervioso central, sistema respiratorio é intestinal. Un niño falleció pesar del tratamiento con penicilina, arsenicales y estreptomicina. El segundo niño finalmente respondió a un tratamiento prolongado de aureomicina.

Fifth Avenue and 100th Street

POLIOMYELITIS AND COXSACKIE VIRUSES IN PARALYTIC POLIOMYELITIS

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STRAINS of Coxsackie virus were first isolated from the feces of two children with paralysis.[1, 2] The recovery of similar agents has since been reported from children and adults with illnesses resembling nonparalytic poliomyelitis or aseptic meningitis,[3–7] from others with little or no evidence of disease[4, 7–14] and from some patients with the clinical syndrome of epidemic myalgia or pleurodynia (Bornholm's disease).[4, 7, 9, 11, 15–17]

A recent communication from this laboratory[10] described the finding of a virus of the Coxsackie group as well as poliomyelitis virus in specimens of feces from each of two children without paralysis. These patients had mild illnesses which were diagnosed as "summer grippe" and the strains of poliomyelitis virus isolated from them appeared to be "of very low virulence for monkeys."[18] The occurrence of both Coxsackie and poliomyelitis viruses in patients with or without paralysis has also been noted elsewhere.[2, 19–21]

This paper presents the results of efforts to recover Coxsackie viruses from children suspected of having poliomyelitis who were admitted to a hospital in New York City during the summer of 1949. Data are given on the isolation and identification of Coxsackie virus from each of two patients with paralysis who at the same time harbored poliomyelitis virus which induced typical paralytic disease in monkeys. Included also in this report are the results of attempts to determine whether the Coxsackie virus and the poliomyelitis virus, which were isolated from one of these two patients, were antigenically related.

MATERIALS AND METHODS

During the summer of 1949 when poliomyelitis was epidemic in New York City,[22] specimens of feces, throat swabbings, and serum were collected from children admitted to the Babies Hospital, New York, who had illnesses resembling poliomyelitis. These materials were stored immediately and kept in a frozen state until tested. The methods used in the preparation and testing of samples as well as the criteria for positive isolations have been described previously.[10, 23]

RESULTS

Specimens of feces or swabbings of the nasopharynx which had been collected during the course of illness from 20 patients suspected of having poliomyelitis were tested for the presence of Coxsackie virus by injection into infant mice. Data concerning these patients are summarized in table 1. They ranged from 8 months to 10 years of age. Ten were males and 10 were females, 18 were white and 2 were Negro. All the patients were found to have pleocytosis of the cerebrospinal fluid during the period of hospitalization although in one case (No. 30) the initial count was normal. All the patients survived. Six of the patients were ultimately discharged from the hospital with a diagnosis of paralytic poliomyelitis and 13 with a diagnosis of nonparalytic poliomyelitis. One of the latter patients had transitory bulbar symptoms and another showed evidence of encephalitis. A

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TABLE 1

SUMMARY OF CLINICAL DATA AND TESTS FOR COXSACKIE VIRUS IN 20 PATIENTS SUSPECTED OF HAVING POLIOMYELITIS

Patient No.	Age Yr.	Sex	Race	Clinical Diagnosis*	Date of First Symptoms 1949	Initial Spinal Fluid			Specimens Tested in Infant Mice			
						White Blood Cells	Per Cent Lymphocytes	Protein mg./100 cc.†	Date Obtained			Results‡
									Feces	Throat Swab	Nose Swab	
2	10	F	W	N.P.P.	9/17	283	95	68	9/29, 10/1			0/8(0)
										9/22		0/9(0)
											9/22	0/9(0)
4	9	M	W	N.P.P.	9/1	490	50	N	9/9			0/9(0), 0/9(0)
5	9	F	W	P.P.	9/5	59	93	40	9/12, 20, 27			*8/9(8), 8/8(3)*
									10/3, 5, 6			0/8(0)
									10/10/12			0/8(0)
									10/23			0/8(0)
6	3½	F	W	P.P.	9/3	18	70	19	9/13, 14			2/9(0), 0/9(0)
8	6	F	N	N.P.P. (Bulbar)	10/4	30	100	26	10/21			0/9(0), 0/9(0)
9	3	F	W	N.P.P.	10/22	33	97	25	10/28			1/8(0), 0/8(0)
										10/27		1/8(0), 0/8(0)
10	3	F	W	P.P. (Encephalitis)	9/17	87	94	+	9/26, 29, 30			*3/3(0)*, 7/7(1)
									10/3, 9			*8/8(2), 8/8(5)*
11	¾	F	W	Encephalitis	9/23	32	85	29	10/4, 5, 6			9/9(1?)§
										10/4		0/9(0)
											10/4	0/8(0)
13	8	M	W	N.P.P.	8/25	20	90	18	8/31			0/8(0), 0/8(0)
19	3	M	N	N.P.P.	9/15	535	99		9/27			0/8(0)
										9/17		0/5(0)
20	8	F	W	P.P.	10/8	230	100	43	10/22, 26			1/8(0)
21	8	M	W	P.P.	9/17	217	100	45	9/22			3/7(1?P)
									10/4, 5, 6			2/8(2?)§
										9/20		0/7(0), 1/7(0)
22	2½	M	W	N.P.P.	10/19	393	33	39	10/26, 30			4/8(0), 0/6(0)§
24	3½	F	W	N.P.P.	9/3	165	99	53	9/16, 18			2/8(1), 0/8(0)
									9/29			8/8(0)§
25	5	M	W	N.P.P.	10/25	200	50	40	11/3			0/8(0)
27	1½	M	W	P.P.	9/18	134	0	N	9/26, 29, 10/5			1/7(0), 0/8(0)
28	8½	M	W	N.P.P.	10/7	500	97	+	10/12			0/7(0), 0/8(0)
29	8½	M	W	N.P.P.	10/18	37	95	34	10/28			0/8(0), 1/9(0)
30	9	M	W	N.P.P.	9/17	2	100	13	9/29			0/8(0)
32	6	F	W	N.P.P.	9/17	99	90	29		9/21		0/8(0)

* N.P.P. indicates nonparalytic poliomyelitis; P.P. indicates paralytic poliomyelitis.

† N signifies normal value; + an increased amount of protein based on results of Pandy test.

‡ Results are expressed as a fraction in which the denominator represents the number of animals used in the test and the numerator those found dead or paralyzed. The number in parenthesis indicates those with signs of paralysis. Definitely positive results are italicized.

§ When suspensions of carcass from these mice were tested for virus by serial passage, the results were negative.

final diagnosis of poliomyelitis was not made in one instance, an 8 month old infant with convulsions and signs of encephalitis but without paralysis.

From the feces of two patients, No. 5 and No. 10, both paralytic, strains of virus were isolated in infant mice and were identified as Coxsackie viruses. Swabbings of the throat from 5 of the 20 patients and from the nose of 2 were also tested with negative results. Swabbings of the nasopharynx were not available from the two patients whose feces contained Coxsackie virus. Specimens of feces from these two patients were also tested in rhesus monkeys for the presence of poliomyelitis virus. In both instances the results were positive, and the monkeys developed severe paralysis with typical lesions in the spinal cord.

The strains of virus which were recovered from these two patients were designated NY5 or NY10 Coxsackie or poliomyelitis virus, respectively. An account of the clinical and laboratory findings in these two patients is summarized below.

Clinical Summaries

Patient No. 5: H. Br., a 9 yr. old white girl, began to develop malaise and anorexia and to complain of pains in the lower back and thighs. Two days later her legs began to buckle beneath her. She was admitted to the hospital 5 days later.

On physical examination she appeared to be well developed, somewhat obese and not in distress. Her temperature was 40.0° C., pulse rate 116, respirations 24 and blood pressure 95/60 mm.Hg. She complained of pain on flexion of her neck. She was unable to flex her left leg and had some weakness in the flexors of the right leg. A knee jerk could not be elicited on the left side and was weak on the right. Kernig's sign was positive.

WBC count was 16.2 thousand/cmm. with 78% polymorphonuclears. The cerebrospinal fluid contained 59 leucocytes/cmm. of which 93% were lymphocytes; the total protein was 40 mg./100 cc., the sugar content was 46 mg./100 cc. and a culture was sterile.

The patient never seemed very sick and became afebrile after approximately 10 days. During the early period of her illness she had pain in her left leg which was somewhat relieved by the application of hot packs. She was found to have weakness involving the erector spinae group and numerous muscles of the left leg including the quadriceps femoris, gluteus maximus, internal and external rotators and adductors of the thigh and also extensors and flexors of the lower leg. She was given physiotherapy and muscle re-education with some improvement. After 2½ mo. in the hospital, she was discharged wearing a leg brace and with instructions to return to the clinic for further observation and treatment.

The diagnosis was poliomyelitis, acute, paralytic, involving the left lower extremity.

Patient No. 10: P. Do., a 3 yr. old female, awoke with a temperature of 38.3° C. During the day she had 3 semi-solid stools but no other complaints. The 2nd day her temperature was normal in the morning but rose to 38.3° C. in the afternoon and was accompanied by headache. The 4th day her temperature reached a peak of 40.0°; the 5th day it was normal. Fever recurred the 6th day and she vomited several times. The 7th day her temperature remained at about 38.9° and a fine vesicular rash was noted to be present over the axillae, inguinal regions and left arm. She complained of burning on urination. In the afternoon she became drowsy and a right facial paralysis was observed. She was admitted to the hospital the following day.

At this time her temperature was 38.3°, pulse rate 110, respirations 22 and blood pressure 115/80 mm.Hg. She appeared to be well-developed and well-nourished but was stuporous and uncooperative with irregular shallow respirations. Her extremities moved following painful stimulation. A right facial paralysis was present and unsustained vertical nystagmus was noted. The tongue was coated, the tonsils and pharynx were hyperemic. A lesion suggestive of herpes was present on the upper lip. Nuchal rigidity was pronounced, and several small nodes were palpable in the anterior and posterior cervical chains. The heart, lungs and abdomen were normal. The tendon reflexes were hyperactive; the Babinski reactions were plantar, Kernig's sign was not elicited. Fine scattered papular lesions were present on the thorax and abdomen especially in the right inguinal region and right axilla. The papules were firm, pinhead in size and on an erythematous base.

WBC count was 7.1 thousand/cmm. A lumbar puncture revealed normal dynamics of the cerebrospinal fluid; the leucocytes totaled 87/cmm., and 94% were lymphocytes. A Pandy test for protein gave a faintly positive reaction. Two days later the leucocytes in the cerebrospinal fluid numbered 33 with 6% polymorphonuclears.

Following admission to the hospital the patient remained febrile for 2 days and was stuporous for 5 days. Thereafter convalescence was uneventful. During her illness weakness of the right abdominal muscles was detected. The facial paralysis was still present at the time of discharge 4 wk. after admission to the hospital.

The diagnosis was poliomyelitis, acute, paralytic, with encephalitis and involvement of the sixth and seventh cranial nerves on the right.

Isolation of Viruses

The strains of Coxsackie virus which were isolated from the feces of these two patients produced fatal paralytic disease in infant mice. In these animals both strains behaved similarly when injected by the intracerebral, intraperitoneal or subcutaneous routes, and were readily maintained by serial passage. The ID 50 titer of virus when injected by either of the latter two routes was approximately 10^{-6}.

Suspensions of feces from each of these patients were also injected into rhesus monkeys by the intracerebral route to test for the presence of poliomyelitis virus. In this manner,

TABLE 2

Isolation of Coxsackie Virus and Poliomyelitis Virus from Feces of 2 Patients with Paralysis

Patient	Specimen Obtained		Results of Tests for Virus*	
	Date 1949	Days After Onset	Coxsackie Virus (in Infant Mice)	Poliomyelitis Virus (in Monkeys)
No. 5	9/12, 20, 27	7 to 22	+16/17 (11)	+2/2 (2)
	10/3–6	28 to 31	− 0/8	+1/2 (1)
	10/10–12	35 to 37	− 0/8	
	10/23	50	− 0/8	
No. 10	9/26–30	9 to 13	+10/10 (1)	+1/2 (1)
	10/3–9	16 to 22	+16/16 (7)	+2/2 (2)

* Results are expressed as a fraction in which the denominator represents the number of animals used in the test and the numerator those found dead or paralyzed. The number in parenthesis indicates those with signs of paralysis.

from both patients, strains of poliomyelitis virus were recovered which produced typical paralytic disease in the monkeys and lesions characteristic of poliomyelitis in their spinal cords. Suspensions of the spinal cords from these infected monkeys were not pathogenic for infant mice. Specimens from other patients in this series were not tested in monkeys for the presence of poliomyelitis virus.

The recovery of poliomyelitis virus as well as Coxsackie virus from each of these patients in relation to the course of their respective illnesses is shown in table 2. It will be noted that in each patient both viruses were present in specimens collected during the first three weeks of illness. In Patient No. 5 poliomyelitis virus was found in the feces during a somewhat longer period and was apparently still present after Coxsackie virus could no longer be detected.

Identification of Coxsackie Viruses

In order to identify the strains of Coxsackie virus obtained from Patients Nos. 5 and 10, neutralization tests were carried out with each of these two strains and seven specific immune sera of proved potency, representing six different antigenic types.[24] Each immune serum was obtained from numerous mice after they had been given repeated injections with a single strain of Coxsackie virus which had been identified previously. The specimens of serum were heated at 56° C. for 30 minutes immediately before they were used in neutralization tests. The mixtures of infected mouse torso which contained approximately

100 ID 50 doses of virus and various dilutions of serum were held for one hour at room temperature and then injected subcutaneously into infant mice.[24]

The results of these tests are summarized in table 3. It will be seen that neither the NY5 nor the NY10 strain was neutralized by the specific antiserum against any of five different types of Coxsackie virus. Both strains, however, were neutralized in high titer by the specific antiserum for Dalldorf's Type 1 Coxsackie virus and by the antiserum for the Easton-2 strain.[21] This latter agent which was isolated in 1949 from a patient in Easton, Pa., has been found to be serologically indistinguishable from Dalldorf's Type 1 virus. The findings indicate that the Coxsackie viruses which were isolated from Patients

TABLE 3

RESULTS OF NEUTRALIZATION TESTS WITH STRAINS OF COXSACKIE VIRUS FROM PATIENTS AND SPECIFIC ANTISERA PREPARED IN MICE AGAINST DIFFERENT TYPES OF COXSACKIE VIRUS

Antiserum Against Coxsackie Virus	Neutralization Titer* Against Virus from Patient	
	No. 5	No. 10
Dalldorf Type 1	>1000	>1000
2	0	0
3	0	0
Conn.—5	0	0
Ohio—1	0	0
Texas—1	0	0
Easton—2 (Type 1)	>1000	>1000

* Titer is expressed as the reciprocal of the highest dilution of serum which neutralized approximately 100 ID 50 doses of virus.

Nos. 5 and 10 in this study were also identified serologically as strains of Dalldorf's Type 1 virus.

COXSACKIE AND POLIOMYELITIS VIRUSES FROM PATIENT NO. 10

Coxsackie and poliomyelitis viruses have been found to differ in several respects including their pathogenicity, antigenicity and host range. As mentioned previously, the NY5 and NY10 strains of poliomyelitis virus, which produced typical paralysis and lesions of the spinal cord in rhesus monkeys, were not pathogenic for infant mice. Nevertheless, the possibility remained that some strains of Coxsackie and poliomyelitis viruses might be antigenically related to each other. If this were ever true it seemed reasonable to consider that such a relationship might more likely be demonstrable with strains of the two viruses which were found together in the same patient. An investigation was, therefore, made with the Coxsackie and poliomyelitis viruses which were recovered from a specimen of feces from Patient No. 10.

Neutralization tests were carried out with the Coxsackie virus and the poliomyelitis virus which were recovered from Patient No. 10 and a number of different sera including immune sera prepared in mice or monkeys against strains of Coxsackie or poliomyelitis viruses. The methods used were similar to those described previously. In tests with the NY10 strain of Coxsackie virus, mixtures of serum and a suspension of carcass from mice

infected with this virus (second mouse passage) were injected into infant mice by the intraperitoneal route; in tests with the NY10 strain of poliomyelitis virus, mixtures of serum and a suspension of spinal cords from three monkeys infected with this virus (first monkey passage) were injected into rhesus monkeys by the intracerebral route. The mixtures of serum and virus were held for one hour at room temperature before injection.

The results of these tests are shown in table 4. It can be seen that serum obtained from normal mice had no neutralizing effect on the NY10 strain of Coxsackie virus, whereas

TABLE 4

RESULTS OF NEUTRALIZATION TESTS WITH COXSACKIE AND POLIOMYELITIS VIRUSES FROM PATIENT NO. 10 AND SPECIFIC ANTISERA PREPARED IN ANIMALS AGAINST COXSACKIE OR POLIOMYELITIS VIRUSES

Antiserum Prepared		Neutralization of	
Against (Virus)	In (Species)	Coxsackie Virus NY10 (in Infant Mice)*	Poliomyelitis Virus NY10 (in Monkeys)†
None	Mouse	0	
Coxsackie NY10	Mouse	1250	0 (2/3)
Poliomyelitis NY10	Mouse	0	
Poliomyelitis NY10	Monkey‡	0	+ (0/3)
Poliomyelitis NY10	Monkey	0	
Poliomyelitis (Brunhilde)	Monkey	0	
Poliomyelitis (Lansing)	Monkey	0	

* Titer is expressed as the reciprocal of the highest dilution of serum which neutralized approximately 100 ID 50 doses of virus.

† Neutralization of approximately 50 ID 50 doses of virus by an equal volume of undiluted serum. Results are expressed as a fraction in which the denominator indicates the number of monkeys injected and the numerator the number which developed poliomyelitis.

‡ This monkey was hyperimmunized by repeated injections of NY10 poliomyelitis virus following acute paralytic disease induced by this agent.

serum obtained from adult mice following repeated injections of this virus caused complete neutralization of the homologous agent even when the serum was diluted more than a thousandfold. On the other hand, immune serum prepared similarly in mice against the NY10 poliomyelitis virus, even when undiluted, did not neutralize the NY10 Coxsackie virus. Immune sera prepared in monkeys against either the NY10 or other strains of poliomyelitis virus also showed no capacity to neutralize the NY10 Coxsackie virus. In similar tests carried out in adult mice immune sera prepared against either the NY10 Coxsackie virus or the NY10 poliomyelitis virus showed no capacity to neutralize the Lansing strain of poliomyelitis virus. As a result of tests carried out in monkeys it was found that the immune mouse serum which in high dilution neutralized the NY10 Coxsackie virus, even when undiluted, did not neutralize the NY10 poliomyelitis virus. On the other hand, the serum from a monkey which was hyperimmunized against the NY10 poliomyelitis virus and which failed to neutralize the NY10 Coxsackie virus did neutralize the homologous poliomyelitis virus.

The results of these tests indicated that the NY10 strains of Coxsackie and poliomyelitis

viruses, although obtained from the same source, were apparently immunologically unrelated to each other.

Relation of Coxsackie Virus to Each Patient's Illness

The recovery of both Coxsackie virus and poliomyelitis virus from the feces of Patients Nos. 5 and 10 during their acute, paralytic illnesses suggested that either one or both of these agents might have caused the disease. In order to obtain additional evidence, specimens of serum collected from each of these patients during the acute and convalescent stages of illness were tested for the capacity to neutralize the strains of Coxsackie virus isolated from them. The results of these tests are shown in table 5.

It can be seen that specimens of serum obtained from Patient No. 5, 7 and 96 days after the onset of illness, had relatively little capacity to neutralize either strain of virus, and this capacity was no greater in the later than in the earlier sample. On the other hand,

TABLE 5

Results of Neutralization Tests with Serum and Strains of Coxsackie Virus from Patients

Patient	Serum		Neutralization Titer* Against Virus from Patient	
	Date 1949	Days After Onset	No. 5	No. 10
No. 5	9/12	7	30	30
No. 5	12/ 7	96	30	30
No. 10	9/26	9	270	90
No. 10	11/30	66	2430	2430

* Titer is expressed as the reciprocal of the highest dilution of serum which neutralized approximately 100 ID 50 doses of virus.

serum obtained from Patient No. 10, nine days after the onset of illness neutralized the strains of virus from Patients Nos. 5 and 10 with titers of 270 and 90, respectively. Moreover, serum obtained 66 days after the onset of illness neutralized both strains in a titer of 2430. This represented an increase in titer of approximately 10-fold against the NY5 strain and of 25-fold against the NY10 strain.

The results of these serologic tests revealed no demonstrable antibody response in Patient No. 5 which could be interpreted as evidence that the strain of Coxsackie virus, found to be present in her feces, was responsible for her disease. On the other hand, evidence was obtained that the Coxsackie virus which was isolated from Patient No. 10 did induce an antibody response in that patient and, therefore, had presumably infected her even though it apparently was not exclusively responsible for her illness.

Discussion

The presence of both Coxsackie virus and poliomyelitis virus in identical specimens from individual patients has been noted on several occasions. These viruses were first found together in specimens of feces collected in 1947 from each of two patients in Ohio

who had mild illnesses diagnosed as "summer grippe."[10] Both of these patients developed during convalescence an increase in antibodies against an Ohio-type strain of Coxsackie virus which was demonstrable by neutralization and complement-fixation tests.[10] The same specimens from these two patients had been tested previously in monkeys by Sabin and Steigman and were found to contain poliomyelitis virus of low pathogenicity for monkeys.[18]

A group of Canadian workers[19, 20] also reported the occurrence of Coxsackie and poliomyelitis viruses in individual specimens of feces from an adult and two children who were members of a single family and from another child who had exposure as a playmate. The specimens were obtained from the children following mild nonparalytic illnesses of approximately 48 hours' duration: the adult had no apparent disease. A young woman in close contact with this family who was mildly ill for two days was found to have poliomyelitis and Coxsackie viruses in successive specimens of feces but not concurrently. Both viruses were also found together in feces collected from a boy with paralytic illness who had no contact with the other patients. Tests with sera from this latter patient suggested that the capacity to neutralize Coxsackie virus increased during convalescence.

Additional evidence was obtained in the authors' laboratory[21] in the course of investigations on an epidemic of poliomyelitis which occurred during the summer of 1949 in Easton, Pa. Specimens were collected during the acute stage of illness from 48 consecutive patients who were admitted to a hospital with a diagnosis of poliomyelitis. Tests for the presence of both Coxsackie and poliomyelitis viruses were carried out with the feces of 36 patients, and both agents were recovered from 20 (56%) of them. The patients who were found to harbor the two viruses simultaneously included 17 with and three without paralysis.[25] Specimens of serum which were obtained during the acute and convalescent stages of illness from two representative patients with paralysis were tested for the capacity to neutralize homologous strains of Coxsackie and poliomyelitis viruses in infant mice and monkeys, respectively. It was found that during convalescence both patients developed antibodies against both viruses.[21]

In the present study specimens which were collected in 1949 from 20 representative paralytic and nonparalytic patients who were suspected of having poliomyelitis during an extensive epidemic in New York City were examined for the presence of Coxsackie virus. Strains of Coxsackie virus were recovered from the feces of two (10%) of these patients. Tests for poliomyelitis virus were also carried out in monkeys with specimens of feces from the two patients in this series who were found to harbor Coxsackie virus. Each of these patients had paralysis; one (No. 10) also had encephalitis, possibly labial herpes and an unexplained rash. In both instances poliomyelitis virus and Coxsackie virus were recovered. Tests with specimens of serum which were obtained from these two patients during the acute and convalescent stages of illness revealed that one but not the other developed a demonstrable increase in neutralizing antibodies against the strains of Coxsackie virus which were isolated from them. Because of the technical difficulties and the fact that specimens of serum early enough in the acute stage for definitive results were not available, similar tests in monkeys for antibodies against poliomyelitis virus were not carried out.

These findings indicate that both Coxsackie and poliomyelitis viruses may be excreted simultaneously by the same patient and that this may not be a rare occurrence at times when both infectious agents are prevalent. Moreover, it has been shown that patients who excrete these two viruses during acute, paralytic illnesses may develop antibodies against

both agents.[21] In the present study a significant increase in the titer of a neutralizing antibody against the homologous type of Coxsackie virus was found in only one of the two patients tested.

Both poliomyelitis and Coxsackie viruses are known to be pathogenic for humans, both are capable of inducing a specific antibody response and both may also be carried by the human host with little or no clinical evidence of disease. Both viruses have been found to have these and other features in common. Nevertheless, they appear at present to be biologically and immunologically distinct and to differ from each other. It is, therefore, difficult but no less important when these agents may be associated with each other, to determine as accurately as possible the role of each in the pathogenesis of disease. This can best be accomplished at the present time by utilizing and evaluating clinical and epidemiologic data as well as evidence obtained in the laboratory.

From the clinical standpoint both agents have been recovered from patients with acute, paralytic or nonparalytic illnesses. On the basis of experience with six laboratory infections[9] and one human volunteer,[16] Coxsackie viruses appear to be capable of causing nonparalytic disease, of which pleocytosis of the cerebrospinal fluid may be a feature. On the other hand, it has not been shown that Coxsackie viruses can also induce in man the typical flaccid form of paralysis which is considered to be characteristic of poliomyelitis. On clinical grounds it seems reasonable, therefore, to consider paralytic illnesses of this type as poliomyelitis until convincing evidence to the contrary becomes available.

Circumstantial but not conclusive evidence may be obtained from evaluations of epidemiologic data. The occurrence of minor nonparalytic illnesses in members of the family or close associates of a paralytic patient should suggest a diagnosis of poliomyelitis, and poliomyelitis virus has frequently been recovered from apparently healthy "carriers" or mildly ill patients under such circumstances. In southern New England during the summer of 1948, the peak incidence of nonparalytic cases with pleocytosis of the cerebrospinal fluid occurred several weeks before the peak incidence of paralytic cases. As a Coxsackie virus was recovered from a number of the nonparalytic patients it seemed possible that an outbreak of nonparalytic disease attributable to the Coxsackie virus may have preceded and overlapped an outbreak of poliomyelitis.[4]

In the past the recovery of poliomyelitis virus from a patient has been widely accepted as evidence of infection by that agent. It is well recognized, however, that the presence of an infectious agent during the course of an illness is not proof of cause. Moreover, in view of the limitations of available laboratory technics, a failure to isolate poliomyelitis virus is not convincing indication of its absence. The same may be said with respect to the isolation or failure to isolate a virus of the Coxsackie group. It may be concluded, therefore, that the isolation of either Coxsackie virus or poliomyelitis virus or both agents from a patient during an acute illness suggests but does not prove that one or both of these agents were responsible at least in part for the associated disease.

Serologic evidence obtained in the laboratory has also been widely used as an aid in diagnosis and to indicate that a particular infectious agent played a causative role. It should be clearly understood, however, that while an antibody response may be acceptable as evidence of infection, it does not prove that the agent which induced the antibody response was necessarily causative of whatever illness happened to occur at the same time. It is obvious that technical difficulties may also limit the procurement or reliability of serologic evidence. This is conspicuously true with respect to poliomyelitis. At present, determinations of antibodies against poliomyelitis viruses, with the exception of the

Lansing type, can only be performed in primates, a limitation which makes these tests difficult, expensive and, for practical purposes, rarely possible to carry out. As a consequence, until better tests are made available the diagnosis of poliomyelitis will almost invariably have to be determined without the aid of serologic evidence. On the other hand, relatively easy and practical methods for measuring antibodies against Coxsackie viruses have been developed, utilizing either the virus-neutralization[24] or complement-fixation[26, 27] technics. This has provided a means to facilitate the recognition and identification of infection by viruses of the Coxsackie group and an aid in the diagnosis of illnesses which may be caused by them.

It may be assumed that present efforts to correlate clinical and epidemiologic data with evidence obtained in the laboratory will be continued, and that new advances will be made in the development of better laboratory technics. As a result, it may reasonably be expected that further progress will also be made in the recognition, identification and differentiation of diseases associated with poliomyelitis and Coxsackie viruses.

Summary

Tests for the presence of Coxsackie virus were carried out with specimens of feces and swabbings of the nasopharynx from 20 infants and children suspected of having poliomyelitis who were admitted to a hospital during the summer of 1949 in New York City.

Both Coxsackie virus and poliomyelitis virus were recovered from feces collected during the course of illness from each of two children with paralysis.

The strains of Coxsackie virus which were isolated from both of these patients were found to be serologically related to Dalldorf's Type 1 Coxsackie virus.

The Coxsackie and poliomyelitis viruses which were isolated from one of these patients were found not to be immunologically related to each other.

Tests with specimens of serum from both patients showed that one but not the other developed, during convalescence, an increase in the capacity to neutralize the strains of Coxsackie virus which were isolated from them.

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SPANISH ABSTRACT

Viruses Poliomielitico y Coxsackie en la Poliomielitis Paralitica

Se investigó la presencia de virus Coxsackie en las heces fecales y secreciones de la nasofaringe de 20 niños presuntamente afectados con poliomielitis, los cuales fueron hospitalizados en la ciudad de New York durante la epidemia del verano del ano 1949. En las heces fecales de dos pacientes con paralisis se demonstró la presencia de una especie de virus letal para el ratón jeven y el cual fué identificado como virus Coxsackie tipo 1, mediante las pruebas de neutralizacion con sueros inmunes especificos. Anticuerpos neutralizantes estaban presente en el suero de ambos pacientes, aunque solo se observó un alza progresiva de los titulos en un solo caso. De estos dos mismos pacientes se obtuvieron especies de virus poliomielitico las cuales produjeron paralisis y lesiones tipicas en monos inyectados intracerebralmente. Este tipo de virus no fué patogenico para el ratón

joven. Los viruses Coxsackie y poliomielitico obtenidos de uno de los pacientes fueron investigados desde el punto de vista de neutralizacion cruzada (cross neutralization tests) en ratónes jovenes y monos, respectivamente, demonstrandose que eran antigenicamente distintos.

Cuando los viruses Coxsackie y poliomielitico se encuentran juntos en un mismo paciente, la evaluación del role de cada agente en la patogenesis de la enfermedad asociada es extremadamente dificil. La ocurrencia de paralisis flacida en pacientes pertadores del virus Coxsackie, puede ser atribuible a su asociación con el virus poliomielitico. No se ha podido todavia demostrar que el virus Coxsackie por si solo sea capaz de inducir paralisis en personas. Basándose en los conocimientos actuales es razonable para el clinico y para el epidemiologista considerar las enfermedades agudas paraliticas tipicas como debidas a la poliomielitis, hasta que haya mas evidencia que pruebe lo contrario.

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TREATMENT OF CHRONIC SHIGELLA INFECTION IN CHILDREN WITH ORAL POLYMYXINS

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UNDER conditions of good sanitation and hygiene, bacillary dysentery is in these days infrequent. When, however, children are placed in an overcrowded environment with poor sanitary facilities, dysentery bacilli are soon widely distributed and the disease occasionally becomes widespread. Institutions for the feebleminded and aged in all parts of the world are heavily infested with Shigella organisms. Under such conditions the control of this infection presents a serious problem.

In the last decade a number of antimicrobial agents have become available for the treatment of Shigella infection. Sulfonamides, streptomycin, aureomycin, chloramphenicol and terramycin all have been shown to suppress dysentery bacilli *in vitro* and to cure acute dysentery effectively. The therapeutic efficacy of these agents has been much less satisfactory in relapsing cases, reinfections and carriers. Although the symptoms of dysentery are controlled, the drugs frequently fail to produce bacteriologic cures.

In bacillary dysentery the infection with Shigella organisms is largely limited to the surfaces of the intestinal mucous membranes. Invasion and widespread dissemination are rare. Chronic superficial infection, on the other hand, is a common sequel to an acute attack of the disease.

An ideal drug for the control of Shigella infection should therefore have the following characteristics: 1. High bactericidal activity, preventing the development of resistant bacterial mutants. 2. Stability, to permit oral treatment, without great loss of antibiotic activity. 3. High concentration of drug on the intestinal surfaces. 4. No irritation to the gastrointestinal tract and no systemic toxicity.

Most of the agents currently employed in the treatment of bacillary dysentery lack in some degree the characteristics outlined. One agent which appears to fit the list singularly well, polymyxin, has received only limited attention in this respect.[1,2]

The polymyxins are a group of polypeptides produced by Bacillus polymyxa. They possess high bactericidal activity against gram-negative bacteria and are very stable. They have limited usefulness in systemic therapy because they are to some extent nephrotoxic and neurotoxic.[3] After oral administration, however, they are not significantly absorbed from the intestinal tract[2,4] and are not locally irritating.

Because of the favorable characteristics of the polymyxins, it was felt worth while to test them in chronic Shigella infections of children where conventional treatment with other antimicrobial agents had been disappointing. This paper reports the results of such a study, in an institution for mentally defective children.

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Materials and Methods

Selection of Patients: The Sonoma State Home, Eldridge, Calif., is an institution for mentally defective children. Its patient population is about 3,500, but its facilities are adequate for the accommodation of only a much smaller number.

Twenty-three patients aged 2 to 11 yr. were selected from 3 cottages in which bacillary dysentery was known to be endemic. Within these cottages there was severe overcrowding and limited toilet facilities and equipment. The number of qualified attendants was inadequate for detailed care of the children. All the patients were mentally defective in various degrees and their habits of personal hygiene were poor.

The 23 selected patients were either asymptomatic carriers of Shigella or were suffering from chronic relapsing infections with acute symptoms. All had 2 positive stool cultures, showing Shigella paradysenteriae (Flexner) in large numbers, in the week preceding their treatment.

Bacteriologic Methods*: Fresh stools were obtained and cultured on S S agar (Difco). Typical nonlactose-fermenting colonies were isolated and identified by the usual methods. The isolated Shigella were typed with type-specific serum. The typing was confirmed in several instances by the Laboratories of the California State Department of Public Health.

Cultures of the Shigella paradysenteriae isolated from 20 of the 23 patients were tested for their *in vitro* sensitivity to polymyxin B or E. A tube dilution method was used, as previously reported.[3] Subcultures were performed on tubes showing no growth in 24 hr., to determine the bactericidal effect of the drug.

Stool cultures were done on all patients prior to starting therapy (2 specimens), on the fifth day of therapy, on the second and fourth day after discontinuing therapy, and thereafter at weekly intervals for 8 wk.

Treatment: The 23 selected patients were placed into isolation wards at the hospital and kept there until the study was terminated. This precaution was essential because of the high carrier rate and environmental contamination in the cottages. Determinations of hemoglobin, WBC count and urinalysis were obtained prior to and after the treatment period. The patients were observed closely clinically. Temperature and pulse were taken 3 times daily. The number and appearance of daily stools was noted and the presence of blood or mucus recorded.

Polymyxin B or E was administered by mouth in daily doses of approximately 15 to 20 mg./kg. for 10 days.† The drug was supplied as white amorphous material in vials containing the equivalent of 100 or 50 mg. polymyxin hydrochloride. It was dissolved in water to give a concentration of 10 mg./cc. and vanillin added to disguise the taste. The total daily dose was given in 3 equal portions, and was taken by the children without difficulty.

Results

To give a background for evaluation of the treatment with polymyxin, the results obtained in the routine therapy of 194 cases of shigellosis during the preceding 12 months at Sonoma State Home are shown in table 1. Various drugs and combinations of drugs were employed with apparent good success in fresh cases. However, in relapsing cases or carriers the average results were poorer. In three weeks of follow-up 37% of patients relapsed clinically or bacteriologically. As shown in table 1 the range of failures with the various drug combinations was 18 to 67%. Had the period of follow-up been extended additional failures probably would have been discovered. In the polymyxin series all three failures occurred between the third and the sixth weeks after termination of treatment.

The over-all results of polymyxin treatment in the carefully studied group of patients

* Acknowledgment is made to Mrs. Ruth McElroy, Bacteriologist at the Sonoma State Home, without whose painstaking efforts and cooperation this study could not have been done.

† The drugs were kindly supplied by Dr. D. S. Searle, Burroughs Wellcome & Company, Inc., Tuckahoe, N.Y.

with chronic shigellosis were better than those previously obtained. Of 23 children treated with polymyxin, 20 (87%) were unequivocally cured, remaining bacteriologically negative for eight weeks after the end of treatment. Had only a three week follow-up period been employed, the apparent "cure rate" would have been 95%.

Details of individual patients are summarized in table 2. The *in vitro* sensitivity of the isolated Shigella flexneri ranged from 0.01 μg./cc. to 0.1 μg./cc. polymyxin B or E, with the following distribution:

Inhibited by 0.01 μg./cc., but not 0.005 μg./cc. 1 strain
Inhibited by 0.05 μg./cc., but not 0.01 μg./cc. 18 strains
Inhibited by 0.1 μg./cc., but not 0.05 μg./cc. 1 strain

TABLE 1

RESULTS OF CHEMOTHERAPY IN ACUTE AND CHRONIC SHIGELLA INFECTIONS

	Acute Cases			Relapsing Cases or Carriers			Total Cases		
	No. Patients	Cured		No. Patients	Cured		No. Patients	Cured	
		No.	%		No.	%		No.	%
Sulfadiazine	46	42	91	22	16	73	68	58	85
Sulfadiazine plus sulfathalidine or sulfasuxidine	48	46	96	24	17	71	72	63	88
Sulfathalidine plus dihydrostreptomycin	5	5	100	11	9	82	16	14	88
Chloromycetin	12	11	92	15	5	33	27	16	59
Aureomycin	5	4	80	6	2	33	11	6	55
Total	116	108	93	78	49	63	194	157	81

Dosages: Most of the patients fell within the weight range of 15 to 20 kg. In these patients, the approximate dosages and medications were as follows:

1. Sulfadiazine: 2 gm. daily by mouth.
2. Sulfadiazine plus sulfathalidine or sulfasuxidine: 2 gm. sulfadiazine plus 10 gm. nonabsorbable sulfonamide daily by mouth.
3. Sulfadiazine plus dihydrostreptomycin: 2 gm. sulfadiazine orally plus 1 gm. dihydrostreptomycin intramuscularly daily.
4. Chloromycetin: 1.25 gm. daily by mouth.
5. Aureomycin: 1.0 gm. daily by mouth.

All the drugs were given over a 10 day period. Where the weights differed from those indicated, modification was made in the dosage.

It was found in all instances that concentrations of 2 to 4 times the inhibiting amounts yielded no growth in subculture, i.e., were bactericidal for the organisms.

In keeping with the high sensitivity of the organisms in the test tube the stool cultures of 18 patients had turned negative on the fifth day of treatment and remained thus during the eight weeks of the follow-up period. Two patients had positive stool cultures on the fifth day of treatment but those were negative at the termination of treatment and remained so for the eight week follow-up period. In the other three cases, 2 of the 3 had positive stool cultures on the fifth day of therapy, negative at the end of treatment, but again positive in the fourth and sixth follow-up week, respectively. The third case became

positive the third week following termination of treatment. Brief summaries of two of these treatment failures are given below.

TABLE 2

CLINICAL SUMMARY OF CASES OF CHRONIC SHIGELLA INFECTION TREATED WITH POLYMYXIN

Patient	Age yr.	Clinical diagnosis	Carrier or relapsing case	Time since 1st positive stool culture	Drugs used previously	Polymyxin treatment (daily for 10 days)	Results of treatment	Follow-up cultures
				Mo.				
L.S.	8	Mongolism	Relapsing case	21	Sulfadiazine and guanidine	Poly E 17 mg./kg.	Cure of acute attack	Neg. for 8 wk.
P.A.	4	Mental deficiency	Relapsing case	4	Sulfadiazine and suxidine	Poly B 16 mg./kg.	Asymptomatic; cured	Neg. for 8 wk.
J.E.	10	Mongolism	Relapsing case	4	Sulfadiazine and suxidine	Poly E 15 mg./kg.	Cure of acute attack	Neg. for 8 wk.
K.C.	1½	Microcephaly	Relapsing case	9	Aureomycin Chloromycetin Sulfamerazine Streptomycin	Poly B 18 mg./kg.	Cure of acute attack	Neg. for 8 wk.
M.R.	10	Mental deficiency	Relapsing case	20	Sulfadiazine Chloromycetin Sulfasuxidine	Poly E 16 mg./kg.	Cure of acute attack	Neg. for 8 wk.
C.S.	8	Cerebral dysplasia	Relapsing case	9	Sulfadiazine Aureomycin	Poly E 16 mg./kg.	Cure of acute attack	Neg. for 8 wk.
R.F.	4	Cerebral palsy	Relapsing case	6	Sulfadiazine Streptomycin	Poly E 20 mg./kg.	Cure of acute attack	Neg. for 8 wk.
M.S.	4	Cerebral dysplasia	Carrier	5	Sulfadiazine and thalidine	Poly E 18 mg./kg.	Asymptomatic; cured	Neg. for 8 wk.
L.P.	6	Mental deficiency	Carrier	5	Sulfadiazine and suxidine	Poly B 16 mg./kg.	Asymptomatic; cured	Neg. for 8 wk.
R.F.	10	Mongolism	Carrier	35	Sulfadiazine and suxidine	Poly B 15 mg./kg.	Asymptomatic; cured	Neg. for 8 wk.
G.D.	7	Cerebral palsy	Carrier	4	Sulfamerazine and thalidine	Poly B 16 mg./kg.	Asymptomatic; cured	Neg. for 8 wk.
G.W.	9	Mental deficiency	Carrier	12	Sulfadiazine	Poly B 16 mg./kg.	Asymptomatic; cured	Neg. for 8 wk.
G.D.	8	Cerebral dysplasia	Carrier	7	Sulfadiazine and thalidine	Poly E 16 mg./kg.	Asymptomatic; cured	Neg. for 8 wk.
J.N.	4	Cerebral palsy	Carrier	7	Chloromycetin Sulfadiazine and thalidine	Poly E 17 mg./kg.	Asymptomatic; cured	Neg. for 8 wk.
R.G.	6	Cerebral dysplasia	Carrier	10	Sulfadiazine Aureomycin	Poly E 17 mg./kg.	Loose stools during treatment; cured	Neg. for 8 wk.
R.B.	7	Cerebral palsy	Carrier	4	Sulfadiazine and thalidine	Poly E 16 mg./kg.	Asymptomatic; cured	Neg. for 8 wk.
J.C.	12	Cerebral dysplasia	Carrier	9	Sulfadiazine	Poly E 16 mg./kg.	Asymptomatic; cured	Neg. for 8 wk.
H.R.	9	Mongolism	Carrier	15	Sulfadiazine and suxidine	Poly E 17 mg./kg.	Asymptomatic; cured	Neg. for 8 wk.
G.H.	2	Cerebral dysplasia	Carrier	4	Sulfadiazine	Poly B 20 mg./kg.	Asymptomatic; cured	Neg. for 8 wk.
A.L.R.	11	Cerebral palsy	Carrier	9	Sulfadiazine and suxidine	Poly E 17 mg./kg.	Asymptomatic; cured	Neg. for 8 wk.
R.G.	2½	Mongolism	Carrier	8	Sulfadiazine and thalidine Chloromycetin	Poly B 17 mg./kg.	Asymptomatic; failure	Pos. in 6th wk.
R.F.	7	Cerebral palsy	Carrier	15	Sulfadiazine and suxidine Aureomycin	Poly B 15 mg./kg.	Asymptomatic; failure	Pos. in 4th wk.
J.D.	7	Mongolism	Carrier	23	Sulfadiazine and suxidine	Poly E 20 mg./kg.	Acute dysentery in 3rd wk.; failure	Pos. in 3rd wk.

Case Reports

Case J. D.: A 7 yr. old boy with mongolism who had positive stools on 11 previous occasions in a period of 20 mo., but who was asymptomatic in spite of a positive culture at the onset of treatment, suddenly developed signs and symptoms of acute dysentery and had a single positive stool culture 3 wk. after polymyxin treatment had been completed. Because of the rapid development of severe watery diarrhea, rectal temperature of 40.8°C. and generalized toxicity with shocklike symptoms, immediate therapy was instituted. This consisted of intravenous fluids containing sodium, potassium and glucose, sulfadiazine intravenously, sulfathalidine rectally and dihydrostreptomycin parenterally. He made a rapid recovery and remained asymptomatic thereafter and had negative stools for the following 6 wk. The Shigella organisms in his pretreatment stools were inhibited by 0.05 μg./cc. polymyxin. He received 20 mg./kg./day.

Case R. F.: A 7 yr. old boy suffering from cerebral spastic quadriplegia was an asymptomatic carrier with stool cultures positive on 4 occasions in 16 mo. After polymyxin treatment stool cultures remained negative for 2 wk., but in the fourth week Shigella organisms were again recovered. His stools remained normal in appearance and he was completely asymptomatic at all times. The Shigella organisms in his pretreatment stools were inhibited by 0.05 μg./cc. polymyxin. His daily dose was 15 mg./kg.

Toxicity of Drug: Careful check was kept on the development of either subjective or objective evidence of drug toxicity, which would indicate significant absorption from the intestinal tract. None of the children developed symptoms of CNS toxicity as seen with the systemic administration of polymyxin.[3] Hemoglobin, WBC count, and urinalysis remained essentially unchanged during and after therapy. There was no proteinuria or hematuria to indicate nephrotoxic effects, from possible drug absorption. Since such side effects may be expected if significant amounts of drug were absorbed over a 10 day period, it must be concluded that absorption was negligible or absent.

Discussion

Acute bacillary dysentery responds well to the usual chemotherapeutic agents.[5–7] This is borne out by the results in 116 fresh cases treated with sulfonamides and antibiotics in the Sonoma State Home, where an over-all figure of 93% clinical cures was obtained. All these individuals had negative stool cultures at the termination of drug therapy and weekly for three weeks. Approximately one fourth of them later relapsed or became chronic carriers.

The epidemiologic control of shigellosis in an institution depends largely on the eradication of carriers and other chronic "shedders." In such persons, however, conventional chemotherapy often fails to eradicate the infecting organisms. Polymyxin was much more efficacious than other antimicrobial agents in the eradication of chronic Shigella infection.

No difference was noted between the efficacy of polymyxin B and E. Treatment with repeated courses appears feasible in view of the lack of toxicity of the polymyxins taken orally and could be expected to improve the results still further. This approach suggests the possibility of treating entire institutional populations with a high endemic incidence of Shigella infection. In the low dose used here the polymyxins did not greatly alter the normal intestinal bacterial flora.[4] There is probably no need to use relatively pure polymyxin, because the cruder, cheaper preparations are likely to be equally effective. Studies with such preparations are being undertaken at present.

The lack of intestinal absorption of orally administered polymyxin has been previously emphasized by Pulaski et al.[4] who detected no blood levels of the drug after daily doses of 200 to 400 mg./kg. Ross et al.[1] likewise found no blood levels after oral daily doses

of 25 mg./kg, but believed that occasionally some polymyxin might be absorbed, since a few of their patients showed proteinuria and a slight transient increase in NPN. In the present study no evidence of significant gastrointestinal absorption was discovered and —in the dosage used—the oral administration of polymyxin is considered entirely safe.

Summary

Many chemotherapeutic agents can alleviate the symptoms of acute bacillary dysentery and suppress the causative organisms. In chronic Shigella infection, however, most agents have only limited usefulness. In an institution for mentally defective children 93% of 116 fresh cases of shigellosis responded to conventional chemotherapeutic measures, but only 63% of 78 chronic cases.

Polymyxin B and E are highly bactericidal for Shigella organisms *in vitro*. These drugs are stable and are not significantly absorbed from the intestinal tract when taken by mouth. Twenty-three children with chronic intestinal infections due to Shigella paradysenteriae (Flexner) were given daily oral doses of 15 to 20 mg./kg. polymyxin for 10 days. Twenty (87%) were unequivocally cured of their infection which had previously resisted therapy with sulfonamides and other antimicrobial agents. No toxic side-effects were observed. Polymyxin appears to be a useful drug for the oral treatment of chronic Shigella infection.

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Spanish Abstract

Tratamiento de la Shigelosis Crónica con Polimyxin

En el tratamiento de la forma aguda de la disenteria bacilar, varios agentes quimioterapeuticos son efectivos en controlar los sintomas y suprimir la infeccíon. De 116 casos agudos de disenteria (Shigella), ocurridos en una institución para niños mentalmente defectivos, un 93% respondieron favorablemente al tratamiento con sulfonamidas y otros agentes antimicrobianos, mientras que de 78 casos de shigelosis crónica, solamente un 63% respondieron al tratamiento.

El control de la shigelosis en instituciones depende principalmente en poder eradicar los portadores crónicos de la enfermedad, en los cuales el tratamiento convencional no es muy eficaz. Polimyxin, un polipeptido estable derivado del Bacillus polymyxa, es marcadamente bactericida contra la Shigella. Esta droga no se absorbe a tráves del canal intestinal cuando se administra oralmente. Los autores trataron un total de 32 niños con infección intestinal crónica debida a la Shigella paradysenteriae (flexner), los cuales recibieron 15-20 mg/kg de polimycin por la via oral por 10 dias. Veinte casos (87%) fueron totalmente curados de la infección, la cual habia previamente resistido a varios otros tratamientos. No se notaron efectos tóxicos. Los autores estiman que el polimyxin promete ser una droga útil para el tratamiento oral de la shigelosis crónica.

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COR PULMONALE IN INFANCY AND EARLY CHILDHOOD

Report on 34 Patients, with Special Reference to the Occurrence of Pulmonary Heart Disease in Cystic Fibrosis of the Pancreas

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PULMONARY heart disease occurs when the right ventricle is put under strain by obstructive lung disease. Once considered a pediatric rarity, this condition has received little notice in the pediatric literature, and the possibility that an infant or child might exhibit cardiac failure secondary to respiratory disease has been given correspondingly meager attention on the hospital wards. Recently an infant was observed in whom pulmonocardiac failure developed during the neonatal period. A subsequent study of the records of patients who came to autopsy in the Babies Hospital over the past 20 years revealed a high incidence of this syndrome. It was found that cor pulmonale often occurs in early childhood, that it is becoming more frequent, and that it can develop in the first weeks of life. This paper presents clinical and pathologic data on 34 patients, all except two of them under 6 years of age.

Congestive heart failure in the neonatal period is not uncommon. Almost invariably it is associated with a severe cardiac defect, developmental in origin. When extensive respiratory disease precedes or accompanies congestive failure the newborn infant is seldom considered to have secondary cardiac damage, even though he may lack good evidence of primary heart disease. The burden of proof is on those who maintain that the pathogenetic factor actually is pulmonary disease, rather than a silent congenital defect in the heart. In a special group of older children, however, pulmonary heart disease occurs with some regularity. Patients with the most extensive lung damage—that associated with fibrocystic disease of the pancreas—often die in congestive failure and show postmortem evidence of right ventricular strain. May and Lowe[1] have reported six cases of this type. At Babies Hospital 27 infants and children with fibrocystic disease showed signs of chronic cor pulmonale at autopsy, and 15 of these patients had clinical congestive failure.

Fibrocystic disease is being recognized with rising frequency, primarily because the diagnosis is increasingly suspected in all infants who begin to cough during or shortly after the neonatal period. The patient mentioned previously, who died at 1½ months of age, belongs in the surprisingly large group whose respiratory symptoms begin in the initial week of life. He first coughed at 3 days of age, had bronchopneumonia at 5 days, and acute congestive heart failure at 11 days. Temporary improvement was followed by a second, and then a third, episode of cardiac decompensation, and he died in his seventh week. At postmortem examination the heart was overweight and the myocardium of the right ventricular wall was thickened; there were no developmental defects. This infant,

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whose case is described below, represented our first recognized experience with neonatal heart failure due entirely to pulmonic disease, and our youngest example of the chronic pulmonary heart.

Case 1.—S.M. was the third child of healthy parents. One older sibling had died of "chronic bronchitis," and there was a normal 2 yr. old brother. The patient, born at full term by breech delivery weighing 4.2 kg., cried well at birth and fed avidly for the first 3 days. On the fourth day he first began to wheeze and breathe heavily. A roentgenogram showed normal lung and vessel markings, with a normal cardiac silhouette. The following day he was discharged from the maternity hospital, but refused all feedings at home and that evening developed noticeable respiratory distress. He was admitted to Babies Hospital at 1 wk. of age.

Initial physical examination showed a large, pale infant, acutely ill and moderately dyspneic. There were white plaques on the buccal mucosa and a fine papular rash on the cheeks and neck. Respiratory rate ranged between 48 and 60, with suprasternal retraction and scattered fine râles in both chests. The heart sounds were normal; no murmurs were heard. Liver was palpable 1 cm. below the costal margin, the neck veins were flat, and the extremities showed good skin tone but were somewhat dusky. Intensive antibiotic therapy was begun. By the next day there was a distinct worsening of the baby's condition. Fine râles had increased, dyspnea was marked, and the infant could not tolerate even brief periods out of oxygen. Dyspnea increased progressively until, on the 13th day of life, there was a sudden change; the baby became deeply cyanotic with gasping respirations and distended neck veins; the liver edge was palpable 5 cm. below the costal border and bubbling râles were heard throughout the chest. Six hours later there was marked facial edema, a further increase in the liver size, and the heart had a gallop rhythm. The heart border could be percussed in the left axilla. The baby became unresponsive, edema spread to involve the entire body, most markedly the feet, and periods of apnea ensued. Following the use of intravenous digitalis, coramine, artificial respiration and finally intracardiac epinephrine, there was gradual recession of the edema, loss of cyanosis, retreat of the liver edge to 3 cm. below the costal border, and a return of normal heart sounds. The chest now showed evidence of extreme emphysema; this remained constant throughout the rest of the infant's life. A chest film taken at this time revealed extensive bronchopneumonia with large patches of obstructive emphysema.

During the next 2 wk. the baby remained relatively improved; his breathing was only mildly dyspneic and he took his feedings remarkably well considering the obvious degree of illness which still persisted. The emphysematous chest and loose cough continued, however, and now the rash, which had remained quiescent during his initial period, spread to involve the arms, legs and abdomen. Candida Albicans was cultivated from these areas as well as from the mouth and anus. A diarrhea of moderate severity developed; the stools were large and mushy and failed to digest gelatin. Despite a low fat diet, pancreatin supplements and numerous additions to his antibiotic therapy the respiratory disability progressed. On the 30th day he had a second episode of congestive failure, this one less severe and of only a day's duration. By this time the chest was fixed in deep inspiration, the heart borders could not be percussed owing to the extreme emphysema, and respiratory excursions were minimal. Progressively he became more dyspneic. As marasmus developed the disproportionately large size of his chest was striking.

Terminally there were repeated attacks of cyanosis, with apnea for increasingly long periods, and an extension of monilial skin rash to involve the entire body. The baby died on the 47th day, during the course of his third episode of heart failure.

Postmortem examination showed the characteristic pancreatic and lung findings of cystic fibrosis. The lungs were markedly distended, covering the cardiac area, with extreme emphysematous changes. The heart was not grossly enlarged but was 20% above average weight, probably owing to the hypertrophy of the right ventricular wall. The latter measured 4 mm. in thickness.

This case, the youngest recorded example of cor pulmonale, illustrates the important clinical features of the syndrome as it is seen in infants. The early onset of obstructive lung disease, the extreme emphysematous change, the explosive type of congestive failure with its unexpected response to desperation therapy, are all characteristic. The patient also demonstrates the difficulty of making a definitive diagnosis of cor pulmonale during life. The consensus of the staff was that he had congenital heart disease underlying his first episode of decompensation, and this opinion persisted throughout his course despite the clinical and roentgenographic evidence that there was, in addition, profound lung disease. Differential diagnosis was not helped by a battery of laboratory and therapeutic tests.

Because he presented a number of unsolved problems concerning the effect of serious respiratory disease on the infant heart, this patient initiated the following study of pulmonocardiac disease.

Definition

In cor pulmonale the right ventricle of the heart is dilated or hypertrophied as the result of pulmonary hypertension. This hypertension, secondary to lung disease, may be acute or chronic, and similarly the lung disease may be of short or long duration. The right ventricle first dilates and then hypertrophies; later there may be a secondary thickening of the left ventricle. But the essential findings are evidence of right-sided overwork combined with the type of lung disease which produces increased intrapulmonary pressure.

Cor pulmonale is not an easily recognized clinical condition. The diagnosis is particularly difficult in the pediatric age group in which measurements are less exact, congenital defects are common, and entities such as acute respiratory infection with fine râles throughout the chest or rheumatic fever with rheumatic pneumonitis may confuse the clinical picture. It cannot be assumed without autopsy confirmation that congestive failure with lung disease always represents cor pulmonale, and heart failure must be considered an occasional complication of cor pulmonale, not a necessary finding.

The usual classification of adult cor pulmonale, which applies equally well to the pediatric level, divides the diseases into three subgroups: acute, subacute and chronic. Acute cor pulmonale is sudden dilatation of the right ventricle secondary to an abrupt rise in pulmonary pressure. Massive obstruction of the pulmonary circulation, as by an embolus or much more rarely by sudden diaphragmatic herniation, is the underlying cause of the adult variety. Comparable precipitating factors are not seen in pediatrics, but acute cor pulmonale has been observed on another basis—the sudden blocking of the pulmonary circulation by intravenous foreign bodies (see Case 2). In acute cor pulmonale the heart shows no structural change except for right-sided dilatation. If the patient does not die immediately, this dilatation is presumably temporary and reversible.

Subacute cor pulmonale is the rarest of the three groups in adults. Recorded instances are limited to a few exceptional causes: the occasional pulmonary embolus that does not cause immediate death nor allow rapid recovery, carcinomatous infiltration of the pulmonary vessels, as reported by Greenspan,[2] and sickle cell anemia causing thrombotic occlusion of the small arteries of the lungs, mentioned by Yater.[3] All these conditions interfere with the flow of blood through the pulmonary circuit, raising the pressure there and thus overworking the right heart. In a study by Brill,[4] multiple small emboli were cited as a cause of subacute cor pulmonale. If the time element alone is considered (these authors give 2 to 9 months as the usual duration), pediatricians have similar situations in a few patients with leukemia and cystic fibrosis.

The bulk of pediatric cases, however, belong to the chronic type of cor pulmonale. These are the infants and children with destructive lung disease who gradually, and often insidiously, show an ever increasing hypertrophy of the right ventricle. Their disease is always progressive; the cardiac damage follows closely the exacerbations of the pulmonary infection and remains stationary with the pulmonary remissions. Death comes after weeks, months or years and may or may not be accompanied by congestive failure.

Historical Review

The literature on pulmonary heart disease in infancy and childhood is quickly reviewed. Andersen[5] first mentioned the occurrence of cor pulmonale in fibrocystic disease of the

pancreas, and others[1] have noted the "dramatic complication" of terminal congestive failure. White[6] described an 11 year old boy whose cardiac disability was associated with pulmonary endarteritis, and has stated that the youngest patient in his experience was a baby 6 months of age with congenital alveolar atelectasis.[7] From such scattered information it is impossible to determine the true incidence of the syndrome in the pediatric population. Cor pulmonale is listed among the rare forms of fatal adult heart disease, and has an incidence of from 1 to 6% of all cardiac autopsies in older patients. Because fibrocystic disease is confined almost exclusively to childhood, it is possible that the pediatric incidence is somewhat higher.

Cor pulmonale may be secondary to many types of chest disease. Table 1, which is based

TABLE 1

COR PULMONALE IN INFANCY AND CHILDHOOD (ETIOLOGIC GROUPING)

I. Disease of Pulmonary Circulation
  A. Thoracic cage deformities
    1. Funnel chest (Coombs[8])
    2. Kyphoscoliosis, postpoliomyelitis (Chapman[9])
    3. Tuberculosis of spine (Edeiken[10])
  B. Distortion of main pulmonary arteries
    1. Diaphragmatic hernia (McGinn[11])
    2. Tumor mass (embryoma, neurofibroma) (White[12])
  C. Distortion of pulmonary arterioles
    1. Leukemia (Brill[4])*
    2. Sickle cell anemia (Yater[3])*
    3. Endarteritis obliterans (White[6])
    4. Primary pulmonary vascular sclerosis (Herdenstam[13])
    5. Intravenous foreign bodies (text)
II. Disease of Pulmonary Parenchyma
    1. Fibrocystic lung disease (Andersen,[5] May and Lowe[1])
    2. Asthma (Schiller[14])
    3. Tuberculosis (Spain[15] and text)
    4. Bronchiectasis (Griggs[16])
    5. Multiple lung cysts (Willius[17])
    6. Congenital alveolar atelectasis (Mallory[18])

* Case reports are limited to adults.

on the primary pathologic change in the chest, summarizes the available case reports in the pediatric literature.

SELECTION OF CASE MATERIAL

The diagnosis of cor pulmonale is established only by anatomic criteria; clinical signs and symptoms are unreliable and only a postmortem examination will definitely exclude a congenital or rheumatic cardiac lesion. To select a criterion of right ventricular strain which is valid in infancy, however, most of the adult standards—comparison of the weights of the right and left ventricles or a measure of the total heart weight—must be discarded. And histologic examination of the individual muscle fibers involves the same ambiguity that is associated with the gross description of a "slightly dilated" or "somewhat hypertrophied" right side of the heart.

The most reliable index of right heart hypertrophy is an increase in the thickness of

the anterior ventricular wall. This measurement, while not ideal, has the closest correlation with the other clinical and pathologic criteria. White[7] states that 3 mm. is the average thickness of the normal adult right ventricle, and in his series of adults with chronic cor pulmonale uses the term hypertrophy to mean a wall 5 mm. or more thick. Spain[15] uses the same figure, adding that the wall of the right ventricle has to be hypertrophied to a greater degree than that of the left. Mallory[18] expresses the opinion that 5 mm. represents an extreme degree of right ventricular hypertrophy in an infant, and would be considered evidence of chronic cor pulmonale even in an adult.

In this study, right ventricular hypertrophy, i.e., right heart strain, was judged by three criteria:

1. A right ventricular thickness of 4 mm. or more in infants (0 to 2 years) and a thickness of 5 mm. or more in children from 2 to 6 years of age.

2. Evidence at postmortem examination of right auricular involvement, consisting mainly of hypertrophy and dilatation.

3. In most cases, evidence of pulmonary artery and pulmonary conus dilatation with thickening of their respective walls.

These standards presuppose the establishment of a "normal" right ventricular thickness for the age groups under discussion. No such norm has been established, measurements ranging from 2 to 4 mm. having been reported as normal. The hearts in this series were measured through a uniform section of the anterior superior wall of the ventricle. In a comparison of the measurements of "normal" hearts in the 20 years' series of 1400 autopsies it was found that the thickness of the right ventricular wall averaged consistently between 2 and 3 mm. in the infants, and from 2 to 4 mm. in the older children. When the thickness of the wall is well over these limits, it is probable that right ventricular strain of considerable magnitude has been present.

By these criteria it was found that 301 cases of the 20 year autopsy series showed right ventricular hypertrophy. Of these, 209 patients had either congenital heart disease or acquired valvular lesions. The remaining 92 cases were analysed to determine the extent of lung disease, and all were excluded which did not have a significant degree. Final figures showed that evidence of chronic cor pulmonale had been observed in 29 patients. Twenty-five had lung disease of the type associated with fibrocystic disease of the pancreas, and each of the other four had a different type of lung disease (bronchiectasis, tuberculosis, interstitial pneumonia and diaphragmatic hernia, respectively). In addition there were two examples of acute cor pulmonale, both due to obstruction of the pulmonary circulation by foreign bodies, and three cases of subacute cor pulmonale associated also with fibrocystic lung disease. These 34 patients represented 2.1%* of all autopsies performed over the period covered by this study and 13% of our total cardiac autopsies.

The patients with fibrocystic lung disease constitute a more or less homogeneous group and will be discussed separately. The six cases in which cor pulmonale was not associated with pancreatic disease will first be briefly presented.

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* This does not, of course, represent the true incidence of cor pulmonale in the pediatric population. The fibrocystic census at Babies Hospital is abnormally high because of the special interest in the disease. More important, however, is its remarkable geographic and racial distribution. To date only 3 Negro children are known to have fibrocystic disease; and whereas since 1938 over 300 cases have been found in New York, in the past 12 years, only 16 cases have been identified at the Charity Hospital of Louisiana in New Orleans.[19]

Case Analysis

Case 2. (Acute cor pulmonale due to plasma contamination.) A.P. This patient was a 19 mo. old girl with celiac disease. Her course was characteristic: she had failed to gain well since birth and at 8 mo. developed moderate steatorrhea. She was a small pale child with a large abdomen and wasted buttocks; her heart and lungs were normal. As her diarrhea progressed it became necessary to bolster her low serum protein levels by giving daily plasma infusions. During one of these infusions she suddenly became cyanotic and the abdominal and neck veins dilated; within 2 min. after the onset of these signs the patient was dead. Investigation of the remaining plasma showed an unusual fine cloudiness in suspension; this was proved, on analysis, to be an inorganic calcium compound. (Calcium chloride had been used to remove fibrinogen from the plasma.) It had been the usual practice to store such plasma in large flasks, and to separate the upper layer of clear plasma by decanting, but recently smaller bottles had been used for storage, making decanting difficult. The plasma in question was injected into rats, which promptly died in the same abrupt manner, showing identical evidence of right heart strain. When the plasma was centrifuged the rats could tolerate massive quantities of the supernatant fluid.*

A similar case of unexpected death in a 3 yr. old girl was subsequently traced back to the same lot of plasma. At autopsy both these children had marked dilatation of the right auricle and ventricle. The cardiac muscle appeared normal, however, and after the incarcerated blood was released the chambers went back to normal size. The right ventricle wall width was 3 mm. in both patients. Microscopically the capillaries of the alveolar walls were engorged, but the offending material was not identified in the sections.

In these 2 cases the calcium precipitate, on reaching the pulmonary alveoli, produced an immediate rise in pulmonary tension and precipitated right heart failure in a matter of seconds. Multiple small emboli and, more rarely, tumor invasion of the parenchyma will similarly raise the intrapulmonary pressure. But the latter conditions exert their effect over a much longer period, hence the heart is given some time to compensate. In the days when transfused blood was first filtered through cotton it was not uncommon to find many cotton fibers in the alveoli of the children who had received several transfusions. There was no evidence that this caused disabling pulmonary or cardiac disturbances.

Case 3. (Chronic cor pulmonale associated with interstitial pneumonia.) A.C., a 14 mo. old girl, was admitted in acute respiratory distress. Her birth and first year had been normal, and except for one episode of otitis she was symptom-free until 5 days before entry when she began to cough and seemed feverish. She did not appear acutely ill until the day before admission when she vomited several times and the cough increased. Physical examination showed a scrawny apathetic infant with cyanosis of the lips and evidence of a widespread respiratory infection. The lungs were hyperresonant, but with some dullness at the left hilum posteriorly, and there were numerous moist râles throughout the chest. The child did not respond to therapy, her respirations increased from 26 to 48, and she died 30 hr. after entry. There was no terminal congestive failure. At postmortem examination the lungs were emphysematous, with large blebs of ruptured alveoli and some patchy consolidation. The heart was grossly enlarged, weighing 60 gm. (normal for this age is 44 gm.). The right auricle, pulmonary artery and right ventricle appeared enlarged; the wall of the right ventricle was 7 mm. thick. Microscopically there was evidence that the pneumonia was of longer duration than the history indicated. The interstitial tissue of the alveolar walls was infiltrated with fibroblasts and large numbers of erythrocytes and leukocytes. The pancreas was normal.

It is surprising that more cases of this type have not been encountered. Death from cor pulmonale does not follow lobar pneumonia, but the diffuse alveolar disease found in infants with interstitial pneumonia is an ideal precursor. Many babies with bronchiolitis or capillary bronchitis suddenly develop edema, dilated vessels and liver enlargement. But this apparent failure is quickly reversible, responds favorably to digitalis, and the patients make a full recovery when the lung disease clears. The case just described represents the author's only example of cor pulmonale following an acute lung infection which was not associated with cystic disease of the pancreas.

Case 4. (Chronic cor pulmonale associated with bronchiectasis.) R.V. was an 11 yr. old girl who had had multiple respiratory infections throughout babyhood. At 2 yr. of age she was admitted to another hospital with "trouble in her lungs" and was treated there for 10 mo. without noticeable

* These studies were done by Dr. Richard L. Day, and are reported with his kind permission.

improvement. On discharge she contracted rubeola and thereafter she coughed almost continuously, bringing up large amounts of green sputum. One year later she entered Babies Hospital. Examination at 4 yr. of age showed a thin, chronically ill girl with early clubbing and roentgenologic evidence of bronchiectasis. Her subsequent course was that of progressively severe lung involvement, necessitating surgical removal of the lower lobe of her left lung at 4 yr. and of the left upper lobe at 5 yr. These procedures afforded little relief; she developed increasing lung destruction with moderate emphysema and the formation of many abscesses, and died on her 15th hospital admission. Shortly before death she became edematous, her liver enlarged and her superficial veins were distended. Following digitalis there was recession of these signs of congestive failure, and she died soon afterwards in an edema-free interval.

Necropsy showed that the remaining right lung had expanded 2 cm. into the left chest. The heart was large, its right side tremendously dilated and hypertrophied. The right ventricle wall measured 5 mm. in thickness. Microscopically the cardiac muscle fibers were hypertrophied. Approximately ⅔ of the lung showed severe emphysema; the rest was consolidated.

There have been 22 deaths from bronchiectasis not related to pancreatic insufficiency over the period studied; this is the only example of marked pulmonary heart disease in that group. It is similarly uncommon in adult medicine, despite the severity and chronicity of the lung disease. Evidence suggests that the relative lack of emphysema protects the heart, and only when these patients with bronchiectasis develop diffuse fibrosis and resultant emphysema do they show cor pulmonale. This girl had a preponderance of emphysematous change in her lungs, lung abscess constituting a minor part of her bronchiectasis.

Case 5. (Chronic cor pulmonale associated with disseminated hematogenous tuberculosis.) A.G., a boy 5 months of age, entered the hospital with the complaint of a cough of one month's duration. Recently he had been noted to wheeze and to breathe rapidly. He was well developed but obviously ill, with mild dyspnea. There were râles and dullness over the upper right chest and RGs showed an opacity in this area. During the next month he had a daily temperature of 38.3° to 40.0°C., the lungs became stippled with minute opacities and tubercle bacilli were cultivated from the thoracentesis fluid. Shortly before death he developed edema of the periorbital tissues, scrotum and subcutaneous tissue of the chest.

At autopsy a large cavity was present in the upper lobe of the right lung, and all lung sections studied showed evidence of hematogenous spread of the tuberculous infection. There was no emphysematous change. The heart weighed 52 gm. (normal 34 gm.), the pulmonary conus was dilated, and the right ventricle wall measured 5 mm. in thickness.

All other reported cases of cor pulmonale associated with tuberculosis have been described in elderly patients with advanced emphysema and fibrosis of the lungs. Cardiac changes in this disease are difficult to evaluate for 2 reasons: first, because there is usually a decrease in heart size in patients with chronic tuberculosis; secondly, because there is also a paradoxic hypertrophy of the right ventricle in 30 to 40% of all cases. Spain[15] considers that secondary emphysema from tuberculous fibrosis is the causative factor; advanced destruction of the lung is probably not necessary. This case combined marked destruction of one lobe with widespread foci throughout the lungs. Emphysema was not a prominent feature.

Case 6. (Chronic cor pulmonale associated with diaphragmatic hernia.) E.H., a male, became dyspneic on the second day of life. Chest RGs showed evidence of a diaphragmatic hernia but operative repair was postponed because of his precarious condition. His dyspnea continued for 3 mo., during which time he was intermittently cyanotic and was described as a feeble whining infant with no exercise tolerance. On examination the trachea was deviated to the right and he retracted at all the rib borders with each inspiration. The left side of the chest was tympanitic and appeared, by roentgenogram, to contain the entire stomach. At later surgery an irreparable condition was found; the entire left diaphragm was absent. He died soon afterwards, at the age of 3½ mo., with terminal congestive failure.

At autopsy the left lung was grealty compressed, occupying only a small part of the left side of the chest. Emphysema was minimal elsewhere in the chest. The heart weighed 37 gm. (average for age, 23 gm.). The right side of the heart was dilated and hypertrophied, the right ventricle measuring 5 mm. in thickness. No myocardial hypertrophy was described.

Nine postmortem examinations on patients with diaphragmatic hernia have been performed. Four of the patients had right ventricular hypertrophy, but all except this infant had certain disqualifying

features. Hiatus hernia is an extremely rare cause of cor pulmonale; the mechanism is not entirely clear but is thought to be lung compression, and emphysema is apparently not a factor. In fact, from this limited series it can be concluded that emphysema is not a *sine qua non* for the later appearance of cor pulmonale, since 3 of these 4 cases showed no significant degree thereof. Conversely, the presence of moderate emphysema does not always lead to pulmonocardiac disease. In 8 postmortem examinations in children with bullous emphysema, there was no instance of right ventricular strain. The disease, in every case, had destroyed a large part of one or both lungs, but the remainder of the lung was normal and was capable of carrying the load without the development of heart strain.

Significant Absences from This Series

It is of some importance in a study of cor pulmonale to mention certain severe lung conditions which have not caused right heart strain. Asthma is the most remarkable of these, for although this disease produces extremes of increased intra-alveolar pressure, and profound lung damage, it has a low mortality, and the asthmatic patient's heart remains singularly free of involvement. This paradox has yet to be satisfactorily explained. One theory is that the reduced filling of the heart, the result of increased intrathoracic pressure, may spare the heart even though the venous pressure is elevated. The heart also tends to remain small despite long-standing asthma. This has been shown by Rubin,[20] who found that cardiac enlargement is rare and, when present, is shared by both ventricles, right ventricle hypertrophy alone being uncommon. When an asthmatic does develop right heart strain he does so only after his lung involvement has been present for many years; 30 is the minimum figure given by most authors. The Babies Hospital has recorded only one death from uncomplicated asthma in the past 20 years. This was a girl 1 year of age who did not have terminal congestive failure and whose heart was observed to be normal at postmortem examination. And all other children who have died with various degrees of asthmatic involvement in their past illnesses have had normal hearts.

Another significant absence is in the group of patients with deformities of the thoracic cage, especially those with funnel chest. Fifteen cases have been seen, but only one death has been recorded and this patient had a normal heart. The other patients showed no disability suggestive of cardiac strain. Again it has been found that in kyphoscoliosis the prime factor in the creation of pulmonocardiac disability is long-standing emphysema. Chapman, Dill and Graybiel[9] showed that the average duration of life after the deformity developed was 30 years. They reported two cases in the teen-age range, boys aged 17 and 18 years who were greatly handicapped, with evident cardiac disability, but still alive.

Other severe lung conditions need be mentioned only briefly. Cor pulmonale has not been seen in infants or older children who died of pertussis, nor has it complicated sickle cell anemia, hyaline membrane or leukemia deaths, even though the last-mentioned patients often have massive chest infiltration. Acute bronchiolitis, or capillary bronchitis of infancy, is of special interest. Since an occasional baby with this acute lung involvement has gone into clinical failure it is reasonable to assume that bronchiolitis may precipitate acute pulmonary heart disease. All these infants of whom we have hospital records have recovered, usually following the use of digitalis, so that there is no postmortem proof of the existence of cor pulmonale.

Occurrence of Cor Pulmonale in Cystic Fibrosis

The etiology of fibrocystic disease remains obscure and its terminology is not yet uniform. The phrase "fibrocystic lung disease," meaning the type of lung change seen

in association with fibrocystic disease of the pancreas, is used for convenience. From the accumulated clinical and pathologic studies, however, it is now possible to predict with reasonable accuracy the course of a baby with fibrocystic lung involvement. He begins with a dry cough, then soon shows clinical signs of bronchopneumonia and progressive emphysema. The final stage is suppuration and cyanosis. Two axioms may be stated: First, that the degree of lung disease determines the patient's degree of morbidity and also his life expectancy; the nutritional state is of minor importance. Secondly, that in general terms the age of onset of cough determines the prognosis; the younger the patient, the worse the prognosis. Both infants and children show this characteristic progression of symptoms, but those who begin to cough during babyhood are more apt to complete the cycle in the shortest time. Over half the total deaths in this survey have occurred during infancy, and all but 15% by the end of the first four years.

This infant group, which includes those who begin to cough in the first weeks or

TABLE 2

AGE WHEN PULMONARY DISEASE FIRST NOTED IN 170 PATIENTS WITH FIBROCYSTIC DISEASE

	Neonatal Period (No. of cases)	Under 1 mo.	1 to 6 mo.	6 mo. or older	Total
Onset of Cough	16	22	70	49	157*
Onset of Bronchopneumonia	4	8	42	86	140*

* Thirteen of the 170 patients have never had a persistent cough and 30 have never developed chronic bronchopneumonia. These figures include 9 infants with meconium ileus, 3 of whom died shortly after birth. Three infants with this condition survived the neonatal period but later died a respiratory or a cardiac death, and 3 are still alive (the oldest is 5 years).

months of life, constitutes the major portion of patients with fibrocystic disease. Among 170 patients studied at Babies Hospital, 108 (64%) had the onset of cough before 6 months of age, and 38 (22%) began to cough before they were 1 month old. A few babies developed the characteristic hacking cough during the first week of life. None, however, was noted to cough before the third day. Of even more importance, since some of these patients may cough for years without ever having serious lung disease, is the time of onset of chronic bronchopneumonia (table 2). Over one third of the patients had clinical and radiologic evidence of bronchopneumonia before the age of 6 months.

In the past six years a new factor in therapy has increased the incidence of right heart strain. This is the widespread use of penicillin, aureomycin and similar antibiotics. These drugs have not only prolonged the course of the disease and improved the prognosis, but they have also changed, as Andersen[5] has shown, the mode of death. Terminal respiratory obstruction with its need for bronchoscopy and tracheotomy has become somewhat less frequent, whereas death in congestive failure—a "cardiac death"—has increased. The manner of death has been observed in 38 patients of the Babies Hospital series. Of these 22 died a "respiratory death," literally drowning in their own secretions; the other 16 had terminal congestive failure. If these deaths are arbitrarily separated into two groups, using 1944 (the year when penicillin came into adequate usage) as the dividing point, a significant change is seen. The number of respiratory deaths is approximately the same in the two periods, but the number of cardiac deaths has trebled since 1944, suggesting some relationship to the new factor in treatment.

Material

Postmortem examination has been made on 36 patients with fibrocystic disease. Excluded are those patients who died at birth from the complications of meconium ileus. Twenty-five of these infants and children showed evidence of chronic cor pulmonale, and three had a course suggesting subacute cor pulmonale, making a total incidence of

TABLE 3

Cardiac Findings at Autopsy in 25 Patients with Cor Pulmonale Associated with Fibrocystic Lung Disease

Age of Patient	Heart Wt. (gm.)	Normal Heart Wt. for Age*	Thickness of Right Ventricle (mm.)
2 mo.	36	21	6
2 mo.	25	21	4
2 mo.	35	21	4
3 mo.	—	23	5
4 mo.	32	27	4
5 mo.	28	28	4
5 mo.	43	28	4
9 mo.	39	37	4
1 yr.	76	44	6
1¼ yr.	45	46	4
1½ yr.	52	48	4
2 yr.	65	56	8
2 yr.	52	56	5
2 yr.	73	56	4
2½ yr.	100	56	6
3 yr.	90	59	5
3 yr.	75	59	5
3 yr.	114	59	6
3½ yr.	117	59	6
3½ yr.	90	59	5
4 yr.	115	73	7
4 yr.	150	73	5
5 yr.	142	85	5
5 yr.	96	85	5
7 yr.	91	100	5

* Coppoletta, J. M., and Wolbach, S. B., Body length and organ weights of infants and children, Am. J. Path. **9:** 55, 1933.

17% of all patients with fibrocystic disease who survived beyond the second day of life. Their case histories do not need repetition since they followed in every respect the variable natural history of the lung disease. The relationship of the duration of lung disease to the mode of death is outlined in table 3. The essential clinical and morphologic findings may be summarized as follows:

Summary of Clinical Observations: When lung disease sufficient to produce cor pulmonale is present, the respiratory symptoms effectively mask all evidence of the laboring heart. This is true no matter what type of lung disease may be present and applies to all age groups, especially to the infant level. Thus cyanosis, clubbing, restricted

respiratory movements, râles, and a low vital capacity are considered signs of cardiac decompensation; yet identical signs will be shown by every fibrocystic patient with advanced lung involvement, whether or not the heart is under strain. Cyanosis was a constant feature of the 28 patients who were later found to have pulmonary heart disease, and clubbing was observed in all patients over 6 months old. An occasional child had the pulmonic systolic murmur described by White,[12] but generally the heart sounds were uninformative and unusually difficult to distinguish, apparently because of the extreme emphysema. This also made percussion of the heart borders unreliable; the point of maximum impulse was often either imperceptible or located in the epigastrium where the pulsation of the lower border of the right ventricle was felt. As the fibrocystic lung disease progressed it became increasingly difficult to separate the respiratory and cardiac signs. Descent of the liver border was due either to enlargement from chronic passive congestion, or extensive fatty infiltration or to displacement, the increased intrathoracic pressure pushing the liver lower in the abdomen. Similar confusion existed regarding the pathogenesis of the venous congestion so often seen in the late stages of fibrocystic disease.

The thoracic deformities secondary to emphysema were striking: the chest became wide and deep at the base; the costal angle increased to well over 90°; the diaphragm descended and abdominal distension, usually a prominent feature in fibrocystic disease, became more noticeable as the ever-expanding chest encroached on the abdominal cavity. Even when an extreme state of emphysema had been achieved the child was apt to survive for many months. At any time, however, there might occur the sudden or gradual appearance of edema, then full-blown cardiac failure and death within hours, or at most a few days. Three patients survived their first episode of congestive failure only to die shortly afterwards in an edema-free interval. These were the exception; the first episode of failure was usually the last. This was in direct contrast to adult experience with cor pulmonale. In the latter group death often did not come for weeks or months after the initial bout of congestive cardiac failure.

Specific treatment of the heart proved ineffective. Relief for the heart could not be obtained so long as the lung disease persisted, and by the time cardiac involvement intervened the child's pneumonic process had reached an irreversible state. Frequently the end was postponed by the use of digitalis, compression bandages applied to the extremities, and positioning, but postponed only a matter of hours. One unusual factor in these cases, however, was their unexpected response to desperation therapy, as exemplified by the infant whose case history was given at the first of this article. This baby had respiratory and cardiac arrest but nevertheless survived for a period of five weeks following the use of cardiac stimulation and intracardiac injections. Apparently the important factor here, and in many similarly unexpected responses, was the injection of the epinephrine-like compounds. These drugs have been used as bronchodilator sprays to alleviate the pronounced wheezing and dyspnea which often herald the end in these children, and many charts contain the note that "following epinephrine (or ephedrine) there was a diminution in the dyspnea and distress." Again the overlapping of the two systems makes this factor in therapy difficult to assess, but the value of epinephrine in adult cor pulmonale has been well proved, and it has a similar place, however minor, in the symptomatic therapy of children. The reversibility thus demonstrated has been only temporary, however, and once cardiac failure occurred the prognosis for recovery was uniformly hopeless.

Summary of Morphologic Observations: The pulmonary lesions of cystic fibrosis have recently received detailed attention,[1,5] so that only the aspects which pertain to the development of pulmonary heart disease will be reviewed. Of these, the emphysematous change is the most important. In all instances the lungs were described as voluminous, hyperexpanded to such a degree that they overlapped the pericardium and met in the midline. The diaphragm was pushed to a low level, usually rib 6 or 7. When the lungs and bronchi were cut they did not collapse in the usual fashion. Microscopically there was fibrous tissue invasion of the alveolar walls, with fibroblasts extending along the septa, and further thickening due to the infiltration of polymorphonuclear cells and lymphocytes. A wide variety of types of lung disease was present in these fibrocystics, but emphysema was constant.

The heart in most instances was not grossly enlarged, in fact it often appeared small compared to the hyperexpanded lungs. The right ventricle and conus were usually dilated, occasionally to a marked degree, and a few specimens showed a moderate degree of left ventricular hypertrophy. Microscopically in about one third of the cases myocardial fiber hypertrophy was described, while the remainder were noted to have normal fibers. The cardiac weight, in all except four instances, was well above the expected normal for that age even though the heart appeared small. The weight, width of the right ventricle, and descriptive morphology are given in table 3.

Other significant postmortem findings were related simply to the degree of congestive failure. This ranged from a minimal amount of change to "marked congestion of all organs." But in no instance was there evidence of long-standing failure, i.e., cardiac cirrhosis of the liver.

Case Analysis

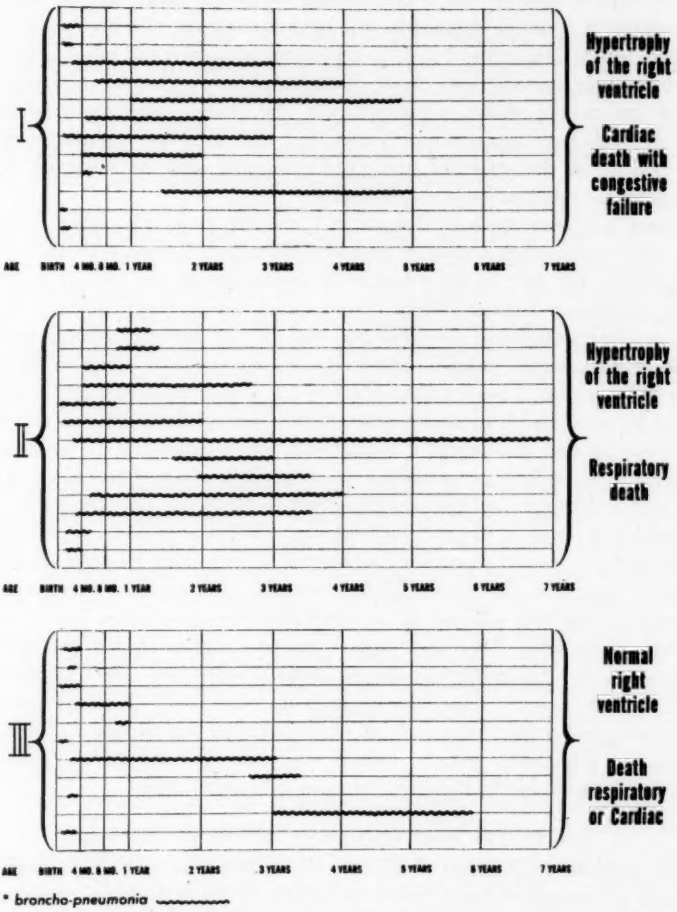
On the basis of the terminal clinical events and of the cardiac findings at postmortem examination, it is possible to divide the fibrocystic autopsy material into three groups. First are those infants and children who, after days, weeks or years of respiratory difficulty, gradually progressed to a decompensated state, then suddenly succumbed to an acute episode of congestive failure. Their courses were most characteristic of classical cor pulmonale, whatever the etiology. At autopsy there was abundant evidence that the heart had been under severe strain.

Some patients never developed clinical congestive failure at any time, even though their lung disease was equal in severity to that of the group above; and though they died a respiratory death there was good evidence of chronic strain of the right heart at postmortem examination.

Finally there were the infants and children whose lung disease was indistinguishable, both in duration and severity, from that of the aforementioned patients but whose hearts entirely escaped evidence of strain. The right auricle and ventricle were normal at autopsy examination. These patients often had terminal edema, liver enlargement and venous congestion, yet showed no evidence of a chronic cardiac disability. They can be regarded, perhaps, as examples of subacute or even acute cor pulmonale—the cardiac failure secondary to overwhelming chest disease which suddenly produced an extreme and irreversible pulmonary hypertension. Circulatory stasis provides a more reasonable explanation for the edema shown by these patients than does hypoproteinemia. In fact, in every instance where appropriate studies of plasma protein concentrations were carried out, the values found were well above the levels usually cited as the edema threshold.

CHART 1

RELATIONSHIP OF CARDIAC FINDINGS AT AUTOPSY TO DURATION OF RESPIRATORY DISEASE* AND MODE OF DEATH IN 36 PATIENTS WITH FIBROCYSTIC DISEASE



The time relationships of the disease in these three groups are seen in chart 1. It is immediately clear that the duration of lung disease bears no constant relationship to the degree of cardiac involvement, nor does the age of onset decree the type of disability. Cor pulmonale may develop in one child in a matter of weeks, whereas in another child it may take years. On the basis of the experience at Babies Hospital it can be stated that chronic cor pulmonale may be expected in approximately 70% of all infants and children who die from fibrocystic disease. Generally speaking, the duration of illness was shorter in those who had no postmortem evidence of chronic cor pulmonale. But a short clinical course was also found in association with extreme degrees of right ventricular hypertrophy, and conversely a long respiratory illness was sometimes associated with complete freedom from cardiac involvement.

Clinical Diagnosis of Cor Pulmonale

In fibrocystic lung disease the symptomatology of the pulmonary and cardiovascular systems overlaps to such an extent that accurate definition during life of the degree of heart involvement is almost impossible. It is hard to assess the presence of even moderate enlargement of the right ventricle since it is an anterior chamber and can enlarge anteriorly without presenting physical signs. Acute dilatation results in extreme enlargement, easily percussible and readily evident radiographically. But chronic hypertrophy, of the degree imposed by pulmonary hypertension, is measured only in a few millimeters and is not directly evident, so that however strongly the diagnosis may be suspected on clinical grounds, anatomic confirmation is always required.

Laboratory tests have not been diagnostic. Circulation times were measured in several patients, with results either normal or somewhat shortened. Venous pressure was elevated in four patients, but only in the presence of obvious congestive failure; at other times the venous pressure was normal. Right axis deviation was frequently noted on the electrocardiograms. Interpretation of its significance was difficult, however, since it might reflect any of three phenomena: normal right ventricular preponderance seen in the first three months of life; a vertical heart pulled down by the descended diaphragm; or a true right ventricular hypertrophy. A consistent polycythemia was not demonstrated, and there was no correlation between the degree of emphysema, polycythemia and cor pulmonale.

In summary, no single symptom or sign was diagnostic of cor pulmonale, and often the onset of cardiac disability could be postulated only in retrospect. This apparently coincided with a sudden decrease in the exercise tolerance. Until late in their course many of the fibrocystic patients showed a surprising amount of activity. They tended to be rather wiry and muscular and, although chronically dyspneic and conservative of excess motion, they played with moving toys and took an argumentative interest in other patients and in the proceedings of the ward. Then there often occurred a sudden change; the child became extremely quiet and disinclined to make the slightest movement. The children seemed to progress from here into a continuously uncomfortable state, querulous and unhappy about anything that required the slightest effort. Whether this alteration in clinical status corresponds to a markedly reduced arterial saturation and increase in carbon dioxide tension (first demonstrated by Borden[21]) remains to be established.

Use of the Roentgenogram in Cor Pulmonale

Roentgenographic examination of these infants and children gives a paradoxic finding: the strained, hypertrophied heart appears to decrease in size as the lung disease progresses. In adult work roentgen technics are of positive value in showing prominence of the right ventricle, occasionally a dilated pulmonary conus, and measurable cardiac enlargement, but similar fine localization of damage is not feasible in pediatric cases. Conversely, it has been found that as the lungs increase in size, the heart tends to shrink in its relative proportions. A common roentgenographic report on the chests of these emphysematous children is that the cardiac shadow appears "small" or "relatively small." The small heart of chronic emphysema has often been noted and a variety of explanations have been given. White[12] and others feel that the heart is more efficient in the early stages of emphysema, that its muscle tone is improved by working against the increased pressure, and the heart itself is spared by the limited pulmonary capacity. Caffey[22] has also pointed out that cardiac hypertrophy (without dilatation) contributes relatively little to the cardiac shadow because the muscle is thickened only a few millimeters at most.

Perhaps the most important factors producing the small heart are those of cardiac compression and, to a lesser extent, cardiac distortion, both of which result from the emphysema. The increased pressure of emphysema exerts its effect along three different lines:

1. The diaphragm is pushed down by the emphysematous lungs. This tends to elongate the heart since it is pulled into a more vertical position by the pericardial attachments to the diaphragm. The cardiothoracic ratio is accordingly decreased.

2. This C/T ratio is further decreased by the abnormal widening of the chest. The lungs, appropriating more space in the thoracic cavity, push peripherally to increase the transverse diameter and push centrally to compress the heart.

3. In emphysema there is an increase in both the venous pressure and in the intrathoracic pulmonary pressure, but the latter is more pronounced. The shift in balance between the air and fluid pressures is of primary importance. Although the rise in venous pressure tends to cause backpressure and the pooling of blood in the heart, there is an even greater increase in the air pressure of the emphysematous lungs. That this pressure imbalance will decrease the size of the heart was shown originally in the Valsalva experiment. The lung changes in cystic fibrosis make such an imbalance a chronic condition.

These factors are diagrammed in figure 1.

Discussion

Among the many unsolved problems of cor pulmonale, whether in adults or children, is the mechanism of cardiac damage. It was formerly believed that the narrowing and thrombosis of the pulmonary arteries (in emphysema, for example) elevated the blood pressure in the pulmonary circuit; the consequence of this was first right ventricular strain, then dilatation and eventual failure. Although there is still general agreement on the rise in pulmonary pressure, recent catheterization studies suggest that the primary pathology lies outside the blood vessels; that they are acted upon secondarily. This explanation, which is in accord with the observed blood flow and pressure studies, postulates that the increased pressure in the alveoli exerts its effect on the smaller blood vessels and capillaries which run through the intra-alveolar septa. This in turn increases the resistance to the flow of blood through these vessels, leading directly to increased strain on the right ventricle. There is further evidence in pediatric medicine that resistance to the flow of blood in based not entirely on anatomic obliteration of the pulmonary vascular bed. Children with the extreme bullous form of emphysema, whose lung disease suggests an anatomic loss of blood vessel area, have been shown by Caffey[23] to follow a benign course, while those with the diffuse form of emphysema, cystic fibrosis being the prime example, may follow a rapidly malignant course and often develop pulmonary cardiac disease.

Cor pulmonale may occur rarely, and unpredictably, in a number of chronic lung diseases, but its frequency is by far the highest in three distinct entities: senile emphysema, the pneumoconioses and advanced bronchiectasis. The common feature of these three conditions is an extreme degree of emphysema. It is likely that a similar pathogenesis exists in fibrocystic disease. Emphysema has been repeatedly indicted as the common factor in adult cor pulmonale: Spain,[15] in 40 out of 60 cases, and Scott,[24] in 32 of 50, demonstrated emphysema as the sole contributing factor. And the combination of factors most likely to produce pulmonocardiac failure has been shown by Griggs and others[16] to be emphysema and bronchiectasis, again a constant combination in advanced fibrocystic

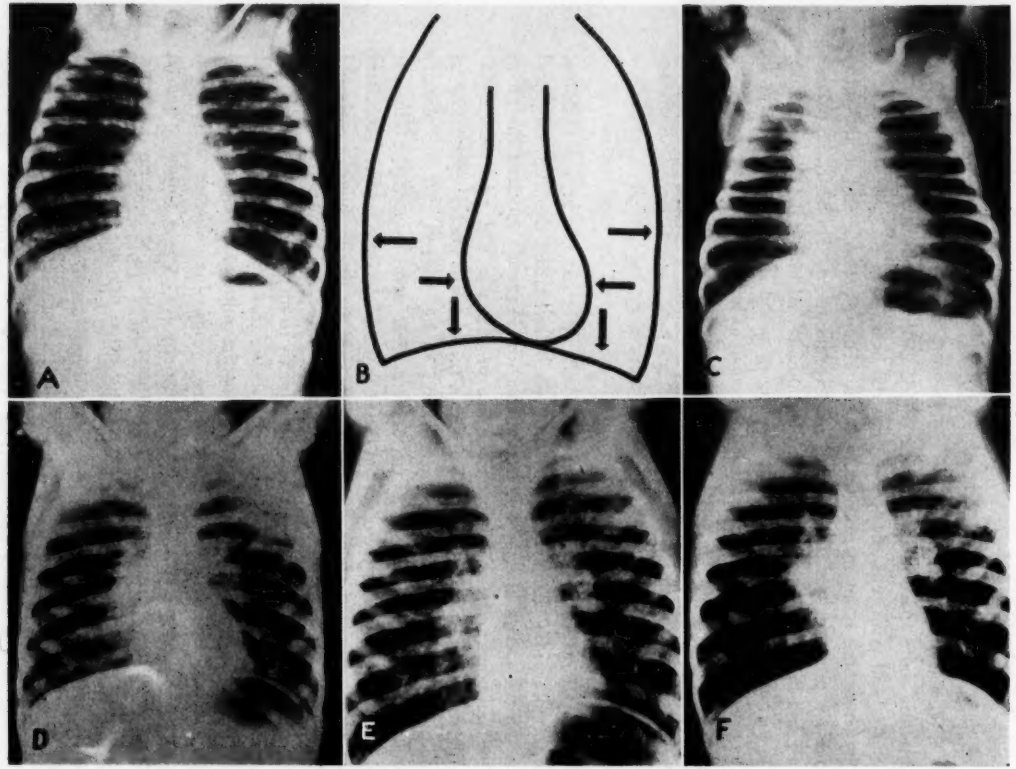


FIG. 1. Heart in Fibrocystic Lung Disease: Figures show relative decrease in apparent heart size with advanced emphysema. (a) Small heart shadow observed shortly before infant died. Autopsy showed cardiac hypertrophy and evidence of chronic cor pulmonale. (b) Diagram of forces tending to diminish heart size: diaphragmatic depression, chest expansion and cardiac compression. (c) Chest film of S. M. (Case 1) taken after second episode of congestive failure. (d-f) Chest films of older child with severe fibrocystic disease, taken at 1 yr. intervals, showing progressive decrease in apparent heart size.

lung disease. A summary of adult experience with pulmonary heart disease shows that emphysema accompanied 95% of all cases. It is not worth while to theorize further, however, since the fibrocystic patient is a poor subject for the study of etiologic factors. His lung disease is a composite of emphysema, atelectasis, bronchiectasis and lung abscess; it is never a "pure type."

The time interval from onset of respiratory disease to cardiac disability is the most variable factor in cor pulmonale. A newborn infant may have clinical evidence of acute cor pulmonale as early as the eleventh day; 3 babies in this series developed chronic cor pulmonale before the third month of life; and 13 cases had appeared before the third year. On the other hand, patients with severe asthmatic bronchitis or advanced silicotic lung disease may live for decades before their cardiac disability becomes apparent. Fibrocystic lung disease may produce chronic right ventricular strain in as short a period as 47 days, or a child may live for as long as 11 years before congestive failure intervenes.

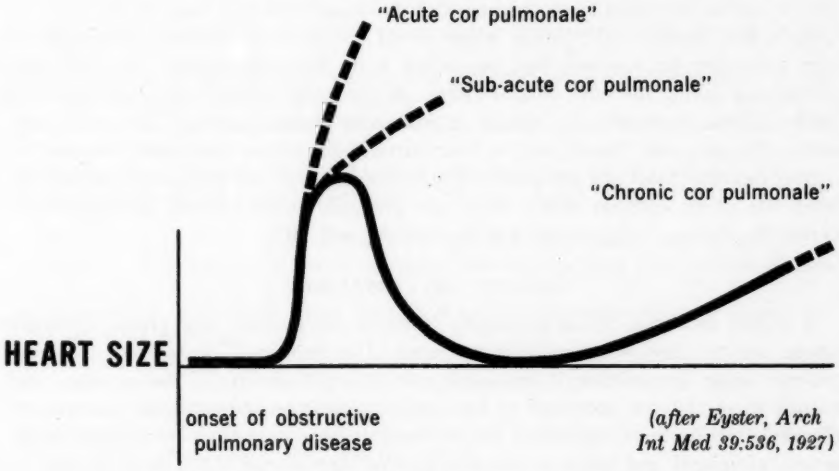


FIG. 2. Development of cor pulmonale: modes of cardiac response.

Animal experimentation may provide some explanation for this variability in individual response. It has been shown[25-27] that when cardiac strain is experimentally produced in dogs by partial ligation of the aorta the heart reacts immediately by acute dilatation and increases in size by 5% or more. A few of the dogs so treated showed progressive cardiac dilatation and soon died, but the majority survived the initial trauma and their hearts returned to normal size in approximately 7 days, even though the source of strain was not removed. Then, as the strain persisted, the hearts showed a gradually increasing hypertrophy which reached its peak in about 100 days. Various figures were given for the shortest period in which demonstrable hypertrophy developed: Stewart[25] noted that hypertrophy was present after only one week of strain; Eyster[26] and Herrmann[27] stated that 19 days was the minimum period.

This analogy should not be oversimplified, since in the one instance the cardiac lesion is the only disability and is experimentally produced by altering the resistance of the peripheral circuit, whereas in fibrocystic disease the entire system is under the strain of

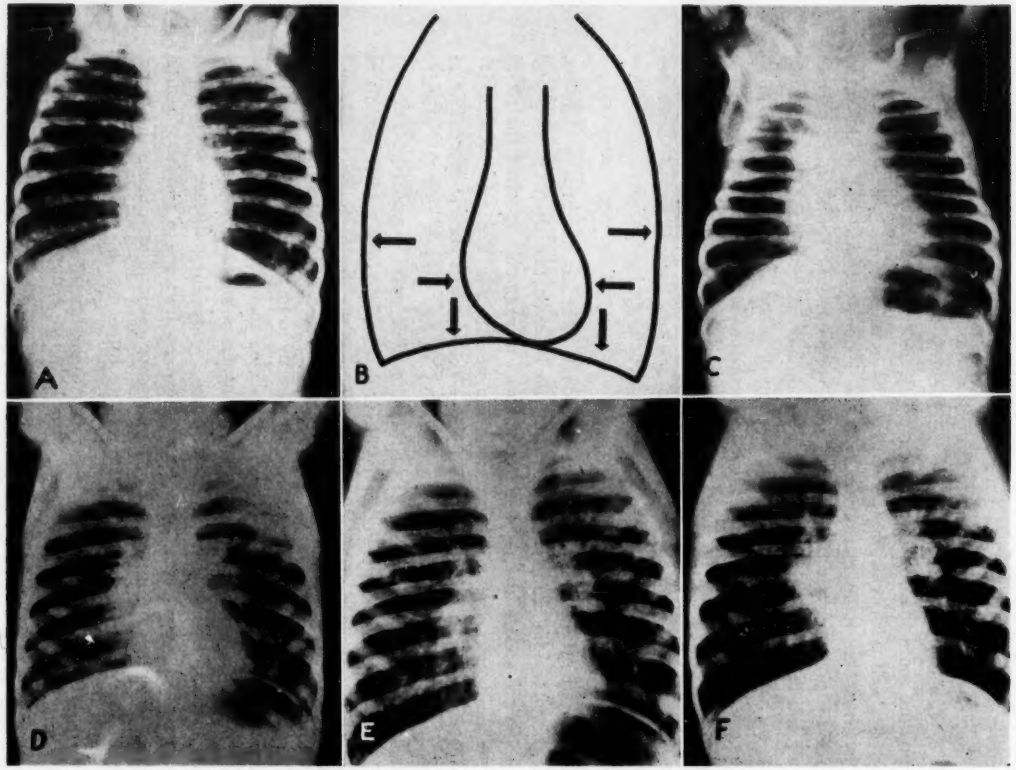
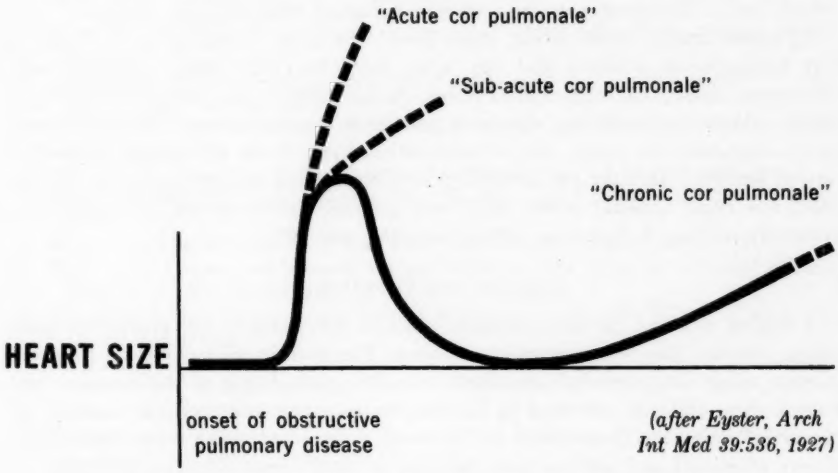


FIG. 1. Heart in Fibrocystic Lung Disease: Figures show relative decrease in apparent heart size with advanced emphysema. (a) Small heart shadow observed shortly before infant died. Autopsy showed cardiac hypertrophy and evidence of chronic cor pulmonale. (b) Diagram of forces tending to diminish heart size: diaphragmatic depression, chest expansion and cardiac compression. (c) Chest film of S. M. (Case 1) taken after second episode of congestive failure. (d-f) Chest films of older child with severe fibrocystic disease, taken at 1 yr. intervals, showing progressive decrease in apparent heart size.

lung disease. A summary of adult experience with pulmonary heart disease shows that emphysema accompanied 95% of all cases. It is not worth while to theorize further, however, since the fibrocystic patient is a poor subject for the study of etiologic factors. His lung disease is a composite of emphysema, atelectasis, bronchiectasis and lung abscess; it is never a "pure type."

The time interval from onset of respiratory disease to cardiac disability is the most variable factor in cor pulmonale. A newborn infant may have clinical evidence of acute cor pulmonale as early as the eleventh day; 3 babies in this series developed chronic cor pulmonale before the third month of life; and 13 cases had appeared before the third year. On the other hand, patients with severe asthmatic bronchitis or advanced silicotic lung disease may live for decades before their cardiac disability becomes apparent. Fibrocystic lung disease may produce chronic right ventricular strain in as short a period as 47 days, or a child may live for as long as 11 years before congestive failure intervenes.



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This analogy should not be oversimplified, since in the one instance the cardiac lesion is the only disability and is experimentally produced by altering the resistance of the peripheral circuit, whereas in fibrocystic disease the entire system is under the strain of

anoxemia, nutritional failure and occasionally severe metabolic imbalance. But the underlying physiology is perhaps of a similar nature, and it may therefore be suggested that cor pulmonale in children with severe lung lesions, especially fibrocystic in origin, may be produced by either of two phenomena (Figure 2):

1. There may be a sudden overwhelming increase in pulmonary tension; the increase occurs over a period of minutes or hours and is of such intensity that the heart is given no opportunity to recover. Accordingly there is progressive dilatation until death intervenes. This severe insult exists in an acute form when certain types of foreign body enter the pulmonary blood, and subacutely when there is a rapid progression of fibrocystic lung damage.

2. If the initial trauma is more gradual in onset, the heart apparently reverses the initial dilatation, compensates for the increased load, and gradually hypertrophies over a period of months or years. The sustained hypertension, however, eventually forces the heart into decompensation. This is seen in a few patients with bronchiectasis and tuberculosis, and in the majority of children with malignant fibrocystic lung disease.

To return, finally, to the patient whose record was given at the first of this paper: it may reasonably be assumed that this infant with fibrocystic disease exhibited both phenomena during his brief clinical career. At the outset of his bronchopneumonia a sudden, almost overwhelming, increase in pulmonary tension occurred. This precipitated cardiac dilatation and failure, but the heart survived the trauma and quickly returned to normal function. Since the pulmonary hypertension recurred and persisted, however, the heart was under constant severe strain and gradually hypertrophied, decompensation eventually reaching a degree that was incompatible with life.

Summary and Conclusions

A higher incidence of cor pulmonale exists in the pediatric age group, especially among infants, than was previously suspected. The majority of cases come from the patients whose lung disease is associated with fibrocystic disease of the pancreas; and because these children now tend to live longer, with improved antibiotic therapy, the chances of seeing this complication are increased. A large proportion (over 70% in this series) of infants and children with this type of lung disease show cor pulmonale at autopsy. This means, statistically speaking, that fibrocystic disease has a high rank among the precursors of pulmonary heart disease in the general population. Other severe lung diseases of childhood, tuberculosis and bronchiectasis, for example, rarely produce cor pulmonale, and the asthmatic patients usually escape entirely.

Approximately half the patients with cor pulmonale have terminal decompensation and die in severe right-sided cardiac failure. This may occur suddenly, only a few days after the first signs of chest disease, or may come on gradually after many years. The duration of disease bears an inverse ratio to the severity of the initial insult. Massive overloading of the pulmonary circulation by blood-borne foreign bodies may cause immediate death, and fibrocystic lung disease may produce such abrupt pulmonary hypertension that the patient survives only a few days. But most infants and children are able to compensate after the initial strain and show a gradual progression to the decompensated state over a period of years.

The diagnosis of cor pulmonale assumes greatest interest at the infant level. It is now clear that otherwise mysterious episodes of infant cardiac failure have been on the basis

of pulmonary disease. In an older child with extensive pulmonary disease and clinical evidence of a failing heart, the presence of proved fibrocystic disease makes cor pulmonale a likely postmortem finding. An infant with the same combination of signs presents a more difficult problem in differential diagnosis since his critical condition often makes direct analysis of pancreatic enzymes hazardous, and stool analysis for trypsin activity may be unreliable under these circumstances. Once the diagnosis is established, however, all effort should be directed toward clearing the chest of infection, since therapy of the secondary cardiac involvement is generally unsuccessful.

ACKNOWLEDGMENT

The writer wishes to thank Dr. Rustin McIntosh, Dr. Richard L. Day and Dr. John Caffey for their valuable assistance. Dr. Dorothy H. Andersen's original work and collected case studies made this paper possible.

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SPANISH ABSTRACT

"Cor Pulmonale" en la Infancia y Niñéz

La insuficiencia ventricular derecha secundaria a afecciones pulmonares (cor pulmonale) no es de ocurrencia rara en niños y a veces puede presentarse aún en el periodo neonatal. El diagnóstico diferencial con las enfermedades congénitas del corazón es frecuentemente dificil especialmente durante los primeros días de nacido. El autor estima que este diagnóstico de "cor pulmonale" es raramente considerado en recién nacidos presentando una insuficiencia cardiaca congestiva, a pesar de la presencia de lesiones pulmonares extensas y la falta de evidencia definitiva de una enfermedad primaria del corazón. En los niños mayores con alteraciones pulmonares profundas tales como las observadas en la fibrosis quística del pancreas, la ocurrencia de una insuficiencia cardiaca puede precedir a la muerte y el exámen necropsico demuestra evidencia de una insuficiencia del ventriculo derecho. Recientemente se acepta que estos efectos de las alteraciones pulmonares produciendo una hipertensión pulmonar, la cual es seguida de una insuficiencia ventricular derecha con hipertrofia miocardica, pueden ocurrir en la más temprana edad y desarrollarse en periodos de tiempo relativamente cortos, frecuentemente en menos de cuatro semanas.

El autor presenta las observaciones clinicas y necrópsicas obtenidas en 34 pacientes (a excepción de dos todos los pacientes eran menores de dos años de edad) de los cuales 28 presentaban lesiones pulmonares tipicas de una fibrosis quística del pancreas. El autor ofrece una explicación para esta incidencia alta del sindrome pulmocardiaco en la fibrosis quística del pancreas comparada con otras afecciones destructivas de los pulmones de niños. Por ejemplo, raramente se observa "cor pulmonale" en pacientes con tuberculosis, bronquiectasia o en asmáticos. La verificación anatómica del diagnóstico de este sindrome es esencial. Clinicamente los sintomas son variados y obscuros, mezcla de signos del aparato respiratorio y cardiaco, y a veces las investigaciones de laboratorio y radiológicas pueden interpretarse erroneamente. Por ejemplo, la sombra radiológica cardiaca disminuye a medida que los cambios pulmonares aumentan.

El diagnóstico de este sindrome tiene un gran interés en la infancia. Muchos cuadros clinicos obscuros de insuficiencia cardiaca en niños actualmente se consideran como efectos de este proceso. Aproximadamente la mitad de pacientes con "cor pulmonale" presentan una descompensación terminal y mueren en severa insuficiencia cardiaca derecha. Esto puede ocurrir rapidamente, a veces solo unos dias después de la aparición de los primeros signos respiratorios o puede desarrollarse gradualmente después de muchos años de evolución. La duración de la enfermedad está en razón inversa a la severidad del insulto inicial. La sobrecarga de la circulación pulmonar puede causar una muerte inmediata y la fibrosis quística del pancreas puede producir una hipertensión pulmonar repentina fatal. La mayoria de los niños pueden compensarse después del ataque inicial y muestran una progresión gradual al estado de insuficiencia en un periodo evolutivo a veces de años. Se señala la relación de los cambios cardiacos observados en la autopsia y la duración de la afección pulmonar.

1635 Chelsea Road

Pediatrics

VOLUME 8 AUGUST 1951 NUMBER 2

AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

THE PRESIDENT'S PAGE

I AM SURE that the majority of our members are not aware of the influence of the Academy in public health and child welfare. For this reason I will recount some of the incidents that have occurred in the past few months which illustrate this.

In May, Dr. Edward Davens, representing our Committee on School Health, went to a meeting in Washington arranged by the National Educational Association to examine the real meaning of citizenship in our country. Excerpts from his report will be published in the News Letter.

Last January, Dr. Reginald Higgons attended a conference on school health in Cleveland, which he reported in full to the Executive Board and which will appear in the agenda of committees published in PEDIATRICS. I would commend this to anyone interested in school health work.

In April, Dr. Stewart Clifford used the report of this same School Health Committee, of which Dr. Thomas Shaffer is Chairman, to modify the school health laws in Massachusetts to conform to its recommendations. If members in states are attempting to introduce modern practices in school health, they are referred to the central office. Dr. Christopherson will be glad to send them a copy of Dr. Shaffer's report.

In February, Dr. Danis' Committee on Hospitals and Dispensaries sent representatives to a meeting in New York, called to discuss the care of contagious diseases in a general hospital. This group represented many organizations, including the American Public Health Association, the American Medical Association, the American Hospital Association, the American Nursing Association, and others. It was financed by the National Foundation for Infantile Paralysis.

Another meeting last December was attended by Dr. Alfred Fischer as a representative of the Committee on Fetus and Newborn. This meeting also was called by the American Public Health Association, and representatives were present there from the American Medical Association, the American Hospital Association, and others. The discussion was on the subject of Clinical Thermometry.

In May, a liaison of the Committee on Immunity of the National Foundation for Infantile Paralysis and our Committee on Immunization and Therapeutic Procedures was established by the appointment of Dr. Joseph Stokes and Dr. Russell Blattner to the National Foundation for Infantile Paralysis Committee on Immunity.

In February, in Chicago, and in Washington in May, Dr. Philip Barba of our Committee on Liaison with the American Medical Association and Dr. Clarence Webb, our liaison representative to the Children's Bureau, met with representatives of many other groups interested in the subject, with the head of the Children's Bureau to discuss possible revival of the E.M.I.C.

The Committee on Cooperation with Non-Medical Groups, of which Dr. Gerald Cline is the Chairman, is sending Dr. Kent Tenny to represent us at Lake Geneva, Wis., this fall at the national conference on family relations.

Also this fall, Dr. Kenneth Landauer, our liaison to the National Foundation for Infantile Paralysis, will be chairman of a delegation consisting of himself, Dr. Hart van Riper, and Dr. Rustin McIntosh, going to the International Poliomyelitis Conference in Copenhagen, Denmark.

It is also a pleasure to note that one of our best liked and highly regarded members, Dr. Katherine Bain, has been recently appointed Associate Chief of the Children's Bureau.

PAUL W. BEAVEN, M.D., *President*

Pediatrics

VOLUME 8 AUGUST 1951 NUMBER 2

SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussion could be free, intelligent and continuous"

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

PEDIATRIC SERVICES UNDER THE HEALTH INSURANCE PLAN OF GREATER NEW YORK

By GEORGE BAEHR, M.D., AND NEVA R. DEARDORFF, PH.D.
New York City

PEDIATRICS, which is concerned as much with disease prevention and child guidance as with orthodox curative medicine, is, in this respect, a bridge between public health and medical care and an example to other branches of clinical medicine. The report of the American Academy of Pediatrics on *Child Health Services and Pediatric Education* explicitly enunciates these higher standards of preventive medical practice to which pediatricians have dedicated themselves but makes it equally clear that they cannot be applied to the general practice of medicine as it is at present organized. It would, therefore, seem desirable to use the information revealed by the Academy's report as a yardstick with which to measure the comparable standards of a comprehensive system of prepaid medical group practice which has endeavored to bring the services of qualified pediatricians, as well as of laboratories, clinical specialists and visiting nurses, to 42,500 families with children in New York City without any financial deterrents to full utilization.

From its inception in 1947, the Health Insurance Plan of Greater New York (HIP) has held to the tenet that a comprehensive program of medical care for families is the best means of providing preventive services and the earliest recognition and treatment of disease. In order to assure medical services of comprehensive scope to its insured families,

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Part of the material in this report was presented before the Section on Public Health of the 145th Annual Meeting of the Medical Society of the State of New York, Buffalo, N.Y., May 3, 1951.

Dr. Baehr is President and Medical Director and Dr. Deardorff is Director of Research and Statistics of the Health Insurance Plan of Greater New York.

HIP adopted the undeviating policy of developing medical group practice. Insurance merely provides the means to this end.

HIP has taken this position because medical group practice, which includes the services of general physicians (family doctors) and qualified pediatricians, can integrate medical care in the best interest of the patient, both in scope and quality and in the basic economy of its administration. For the physicians, it provides a better setting in which to practice medicine. The close daily association with colleagues possessing other skills and experience provides a continuing education for the participating physicians. They enjoy vacations and can take time for postgraduate training without loss of income and they are free at night and on weekends except when on alternate duty for their associates. There is no billing of individuals for services rendered.

Under a prepaid plan such as HIP the medical groups can be remunerated entirely on an annual per capita basis for their comprehensive services to families. There are no extra charges to the consumer which, in ordinary practice, limit utilization of available clinical and laboratory resources. This freedom from financial deterrents offers the participating physicians and their patients the maximum opportunity for preventive medical practice and early disease detection, the objective of the American Academy of Pediatrics. The practicality of the Plan has been demonstrated by its growth within four years to an enrollment of 260,000 people, by the fact that it has been operating "in the black" for the past 2½ years, has ample reserves, and is paying the 950 physicians in its 30 medical groups about $6,500,000 a year for the medical care of a little over a quarter of a million insured persons. The organization of the individual medical groups and details of their operation have been reported in the *Journal of the American Medical Association,*[1] June 17, 1950, and will be omitted in this paper except as they relate to pediatrics.

Pediatricians in HIP

The 30 medical groups serving HIP enrollees have 62 pediatricians. Seven of them serve in two medical groups, making a total of 69 pediatric posts in the 30 groups—an average of something over two pediatricians per group. Four are women. Thirteen of the pediatricians are under 35 years of age; 34 are between 35 and 44; nine are between 45 and 54; and six are over 55.

The age distribution of these pediatricians deviates from that of the 3,430 pediatricians described in the study of the American Academy of Pediatrics as follows:

	American Academy of Pediatrics	HIP
Total	100.0	100.0
Under 35 yr.	17.8	21.0
35-44	36.8	54.8
45-54	29.0	14.5
55 and over	16.4	9.7

The HIP groups have proportionately a few more pediatricians under 35, considerably more who are between 35 and 44, and fewer over 45.

Of the 62 pediatricians, 40 are qualified diplomates of the American Board of Pediatrics. This is a considerably higher proportion (64.5%) than was found in the American Academy study (51.4%). In 28 of the groups the chiefs of pediatrics are diplomates of the American Board, as are all but one of the men over 50. The remaining 22 of the

62 pediatricians, mostly younger men, have been qualified under the rules of HIP's Medical Control Board, which require residency training and indoor hospital staff appointments in an approved hospital or other evidence of professional competence and years of experience in the specialty.

The medical groups, all but one of which are medical partnerships, are remunerated through capitations which are now about $24 per enrollee per year. They receive the capitation from HIP for every member of an enrolled family, without regard to family size, although families pay the identical premium to HIP whether they have one child or 12 children. It provides sufficient gross income so that the groups on reaching the present average enrollment of 9,000 or more have sufficient funds to pay their participating physicians at an average rate of compensation comparable to that of non-HIP private practice. This represents net compensation after deducting the operating expenses of the group's medical center (calculated at 40% of gross income). Usually the specialists are paid at a somewhat higher rate than the general physicians, but the disproportion between the earnings of the family doctor and the specialist is by no means as great as in ordinary practice. In addition, most of the HIP physicians engage in a variable amount of non-HIP private practice either outside the group or in the group's medical center. As a group's subscriber enrollment increases, more of the participating physicians find it necessary to devote most of their attention to their HIP responsibilities.

Child Population Covered in HIP

Of HIP's total enrollment on March 1, 1951, of almost 260,000 persons, 24.5%, or about 63,500, were children under 15 years of age. Of those under 15 years, 36.0% were under 5 years, 34.6 were between 5 and 9 years, and 29.4 were aged 10 to 14. In borough distribution, we find 12,433 of these children in the Bronx, 23,103 in Brooklyn, 18,282 in Queens, 2,015 in Richmond, and only 7,652 in Manhattan. (See table 1.) These 63,500 children are members of 42,500 families. Family coverage for insurance purposes in New York includes only the children under 18 years. Of the children under 15, it is estimated that 24% are in families with one child covered; 40 with 2 children covered; 20.9 with 3 children covered; 9.0 with 4 children covered; and 6.1 in families with 5 or more children covered. One HIP family has 12 children—14 members in all. Altogether HIP has had an experience of 154,027 years of coverage of children under 15 years.

Over 5,500 children born into HIP since it was established four years ago survived their first month—they are what Quakers might call birthright members. Any child born to a woman covered by the HIP family type of contract is entitled to full pediatric coverage from the moment of birth. As has been said, after the firstborn, all families pay the same premium rates, but the medical groups receive full capitation for each new member of the family. They therefore have a good incentive to report them promptly to HIP.

Availability of Pediatric Services

The report of the American Academy of Pediatrics revealed that New York leads all the states except the District of Columbia in the availability of pediatricians in private practice.* Pediatric service, however, is four times more available to HIP children than

* According to the report of the American Academy of Pediatrics, for each 1,000 children under 15 years, there was .10 pediatrician in the United States, .35 in the District of Columbia, .24 in New York State. HIP has .98 for each 1,000 children under that age.

to the children of New York State generally. According to the American Academy report, all but a small fraction of the child population of the State is in greater or lesser metropolitan areas or adjacent thereto. If we assume that all of the pediatricians in New York were located in these areas, the child population residing in metropolitan areas in 1945 had one pediatrician for 3,841 children. If we further assume that pediatricians live

TABLE 1

AGE DISTRIBUTION OF HIP POPULATION, 5 YEAR AGE GROUPS FOR CHILDREN UNDER 15 YEARS OF AGE BY BOROUGH OF MEDICAL GROUP LOCATION, MARCH 1, 1951

Borough of Medical Group Location	All Ages	Enrollment by Age Group*				
		15 yr. and Over	Total Under 15 yr.	Under 5 yr.	5–9 yr.	10–14 yr.
Total HIP						
No.	257,280†	193,795	63,485	22,868	21,950	18,667
Per Cent	100.0	75.5	24.5	8.8	8.5	7.2
Bronx						
No.	50,542	38,109	12,433	4,043	4,498	3,892
Per Cent	100.0	75.4	24.6	8.0	8.9	7.7
Brooklyn						
No.	86,528	63,425	23,103	8,307	8,047	6,749
Per Cent	100.0	73.3	26.7	9.6	9.3	7.8
Manhattan						
No.	44,490	36,838	7,652	* 3,114	2,447	2,091
Per Cent	100.0	82.8	17.2	7.0	5.5	4.7
Queens						
No.	68,473	50,191	18,282	6,642	6,299	5,341
Per Cent	100.0	73.3	26.7	9.7	9.2	7.8
Richmond						
No.	7,247	5,232	2,015	762	659	594
Per Cent	100.0	72.2	27.8	10.5	9.1	8.2

* Distribution based on percentages in each age group as of July 31, 1950. From that date to March 1, 1951, total HIP enrollment increased 3.1%

† Excludes 1,890 persons living outside the 5 boroughs who are not attached to any medical group.

exclusively in *greater* urban centers, there is still only one for 2,533 children resident in such areas. In HIP there is one pediatrician for 1,025 enrolled children under 15. In other words, if we assume that all the pediatricians live in the large urban centers of the State, there are about 2½ times as many pediatricians available to the HIP child population as are found in large urban populations in New York State.

POLICIES IN THE ADMINISTRATION OF PEDIATRIC SERVICES

The basic contract between HIP and the medical groups and the conditions laid down by its Medical Control Board require the groups to meet specific professional standards. They may, however, adopt higher standards of professional services and physical resources than those set by regulations. Experiments looking toward improvements in service and in efficiency in the rendering of service are constantly encouraged by the

Medical Department of HIP through its three supervisory divisions, the Division of Professional Practices, the Division of Administrative Practices, and the Division of Preventive Services.

Orginally the groups were free to make their own arrangements for the division of labor between pediatricians and family physicians. These policies varied at first among the various medical groups all the way from using the pediatrician only for cases on which the family physician wanted consultation, to the assignment of all children under 14 years of age to the pediatricians of the group for routine care. Upon the publication of the report of the American Academy of Pediatrics in 1949 and on motion of a medical director of one of the medical groups, then a member of the Medical Control Board, that body adopted a standard requiring that thereafter every child under one year of age should be in the care of the pediatrician. All 30 groups now comply with this regulation; seven groups actually keep their enrolled children under the care of the pediatrician through the twelfth year and two through the thirteenth year.

The distribution of the medical groups in each borough according to these policies, together with the proportion of the child population under 15 years in the respective groups in each borough, are shown in table 2.

When the entire child population enrolled in HIP is reviewed, we find that 48.5% of the children are under pediatric care to school age and about 32% have routine pediatric care to puberty. The other half of the children all have such care through their first year, with a few continuing through the second year, and pediatricians are available thereafter on a consultant basis to age 13.

The differences in these policies among the several boroughs in New York City are striking. In Queens, Staten Island, and the Bronx, most of the medical groups have policies which assign only children under one year to the pediatricians for routine care. At the other extreme is Brooklyn, where all seven of the medical groups assign all children up to school age to the pediatricians and five groups carry this service through ages 11 and 12. The medical groups in Manhattan have policies which run the gamut of all four classes. Why it is that the boroughs in New York City differ so markedly in this respect is not clear. Later in this paper we shall have a little more to say about these pediatric policies.

The variations in pediatric practice within HIP would seem to reflect differing attitudes of the medical profession as to the appropriate assignment of children to pediatricians for general health supervision—but with this difference: The general physicians (family doctors) in HIP who take care of children after their first or second year can refer them to pediatricians at any time and for any reason without fear of losing a patient or a family and without any cost to the subscriber.

Office, Home and Hospital Calls by Pediatricians

The different patterns of pediatric practice are reflected by the data on office, home and hospital calls of pediatricians functioning under each of the several pediatric policies. In table 3 is set forth the 1949 full year's experience in pediatric service under each of the several policies then in effect.

It is apparent from this record that the pediatricians who serve only as consultants make considerably fewer home calls than those who are responsible for general care. When visiting in the home, the latter may see more than one child, especially if he is interested in well-child supervision, and may thus multiply his home visits. But the differences are so great as to suggest that among pediatricians themselves there are divergent patterns

TABLE 2

MEDICAL GROUPS AND ENROLLEES UNDER 15 YEARS OF AGE DISTRIBUTED ACCORDING TO BOROUGH AND MAXIMUM AGE FOR ROUTINE CARE BY PEDIATRICIAN

HIP, MARCH 1, 1951

Borough	Total		Maximum Age for Routine Care by Pediatrician											
			12 mo.			24 mo.			5, 6, 7 yr.			11, 12 yr.		
	Medical Groups	Enrollees*	Medical Groups	Enrollees		Medical Groups	Enrollees		Medical Groups	Enrollees		Medical Groups	Enrollees	
				No.	Per Cent of Total		No.	Per Cent of Total		No.	Per Cent of Total		No.	Per Cent of Total
Total HIP	30	63,485	14	31,947	50.3	2	740	1.2	5	10,571	16.6	9	20,227	31.9
Bronx	5	12,433	4	9,595	77.2	—	—	—	1	2,838	22.8	—	—	—
Brooklyn	7	23,103	—	—	—	—	—	—	2	6,048	26.2	5	17,055	73.8
Manhattan	10	7,652	3	2,755	36.0	2	740	9.7	1	985	12.9	4	3,172	41.4
Queens	7	18,282	6	17,582	96.2	—	—	—	1	700	3.8	—	—	—
Richmond	1	2,015	1	2,015	100.0	—	—	—	—	—	—	—	—	—

* Children under 15 yr. of age, as of March 1, 1951, according to age distribution on July 31, 1950.

of practice. In one group of men we see the concept emerging of close contact with families, in the other, the concept of the consulting specialist working largely in his office with the patients who come to see him.

The effect of the selective policy also appears from the hospital visits. The consulting pediatrician who has only referred patients sees mostly the complicated cases and performs a larger proportion of his service in the hospital.

The American Academy report gives the proportion of office, home and hospital calls

TABLE 3

SERVICES RENDERED BY HIP PEDIATRICIANS BY PLACE SEEN, DISTRIBUTED ACCORDING TO MEDICAL GROUP POLICIES ON PEDIATRIC CARE, CALENDAR YEAR 1949

Maximum Age for Routine Care by Pediatrician*	Number of Medical Groups	Pediatricians' Services by Place Seen							
		Total		Office		Home		Hospital	
		No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Total HIP	26	74,339	100.0	46,457	62.5	21,794	29.3	6,088	8.2
12 mo.	4	2,016	100.0	1,518	75.3	382	18.9	116	5.8
24 mo.	2	586	100.0	407	69.5	131	22.3	48	8.2
5, 6, 7 yr.	4	16,183	100.0	9,382	58.0	5,427	33.5	1,374	8.5
11, 12 yr.	7	43,678	100.0	25,728	58.9	14,861	34.0	3,089	7.1
Consultation only*	9	11,876	100.0	9,422	79.3	993	8.4	1,461	12.3

* During 1949, although not subsequently, 9 medical groups were still using general practitioners for routine pediatric service; the pediatricians in those groups served as consultants.

for the pediatricians of the United States as 62.2% for office calls, 16.7 for house calls and 21.1 for hospital calls. This indicates that the truly sick children received the major attention of the country's pediatricians in contrast to HIP's experience, which reveals that only 8.2% of the total pediatric services are performed in hospitals when routine pediatric care is more freely available to the child population.

QUALITY OF PEDIATRIC CARE

When HIP had been in operation for two years, the medical groups and the central organization decided that it would be well to review in detail the quality of the services being given the enrolled subscribers. Dr. Henry Makover was employed to examine the services of each group and to rate each medical group in reference to the others. It was not possible to rate them in reference to medical care in the city as a whole, because there are as yet no criteria by which to judge medical care in the private practice of medicine. Several medical groups in HIP are operated under the auspices of teaching hospitals or have staffs recruited from these institutions. These groups provided a sort of benchmark which could be used for the purposes that we had in mind. In order to arrive at his ratings, the investigator made field studies during which he examined 100 case records in each of 26 medical groups. The cases were chosen as a straight series from the utilization reports filed by the medical groups with HIP's Division of Research and Statistics. The 100 cases in each group consisted of 25 health examinations of supposedly well

persons, 25 pediatric cases, 25 cancer cases, and 25 records of persons with gastric disorders.

In examining the records of the pediatric cases, the investigator looked not only for the quality of the care given sick children but also for all of the evidences of an alert program of preventive service, of the fostering of normal growth and development, and of full utilization of the resources of the group in the correction of physical defects.

As the ratings took form from this field study, the investigator found a higher degree of uniformity in the quality of the pediatricians' services in all the medical groups than was true of the three other categories of clinical material under investigation. He was able to assure the Board of Directors and the Medical Control Board of HIP that the services rendered by the HIP pediatricians conform in general to acceptable pediatric standards.

Besides this special effort at an appraisal of the quality of pediatric care, the medical department of HIP maintains close and constant contact with the work of the medical groups through a regional medical officer for each borough of the city, a corps of administrative assistants, and a Division of Preventive Services and Health Education. Unlike indemnity insurance organizations, which are concerned only with aid to the patient in paying his doctor for a serious illness, HIP is in essence quite as much a community medical service as it is a plan for prepayment. A subscriber who is not satisfied with the care he receives from his doctor may complain to the director of his medical group or to HIP itself. About two complaints per month per 10,000 enrollees are received at the central organization. Often these do not relate to the quality of medical care but to some detail of administration. Upon request, enrollees are free to transfer from one group to another and from one general physician or pediatrician within the group to another. A relatively small proportion of them do so for reasons of dissatisfaction with the care they are receiving, and people in New York City are not without medical sophistication, especially as regards their children. Their attitude may be judged by the fact that terminations of contracts by subscribers for all causes, including removal from the city, changes in employment, loss of employment, failure to convert the insurance on reaching 18 years of age, and dissatisfaction have averaged about 8% a year during the past four years.

Utilization of Physician Services by Children

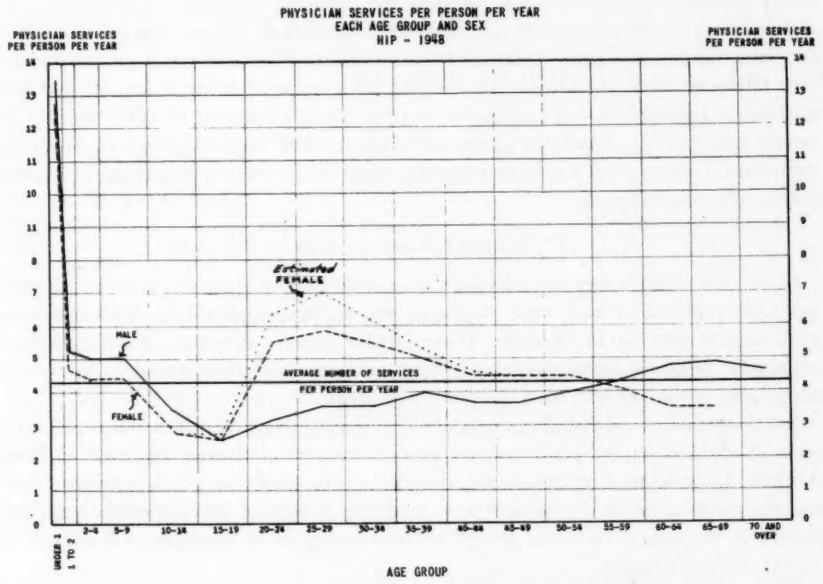
Since the beginning of HIP's operation four years ago, every medical service rendered by a general physician, pediatrician, or other specialist has been reported to HIP headquarters, where it has been recorded by means of a punch card code. These entries carry information which identifies the patient and his family and give his diagnosis, the place at which he was seen, the specialty of the attending physician, and the general nature of the service rendered, such as preventive service, surgery and other diagnostic or therapeutic services. On the basis of these data, utilization rates can be readily compiled for the total persons covered by HIP, for those enrolled with each medical group, and for those of each sex and age. For special studies such as our recent report to the International Congress on Obstetrics and Gynecology on Maternity Services under the Health Insurance Plan,[2] supplementary information is assembled from the underlying clinic records of the medical groups.

Age-specific utilization rates were computed for the 1948 experience when there were 117,000 enrollee years and 500,000 physician services, as reported in the *American*

Journal of Public Health.[3] The chart from that article is of such general interest that it is reproduced here. (See chart 1.)

These rates include all physician services. In 1948 some of the babies received their routine health supervision from family physicians. Nevertheless, the record makes it abundantly clear that the babies and young children in HIP are receiving physicians' services in good measure. These figures reveal that the parents in HIP families are bringing their children to the HIP physicians for health supervision and preventive services as well as for medical care when they are ill. The general rate of 13.1 services per enrolled

CHART 1



child under one year conceals some differences among the medical groups but these were not very wide.

The high rate of utilization of pediatricians' services for infants in the first year, and especially in the first months of life, is probably at least in part responsible for HIP's low neonatal mortality rate of 9 per 1,000 live births compared with a rate of 20 per 1,000 for New York City as a whole, 20.7 per 1,000 for New York State, and about 25 per 1,000 for the country. Other contributing factors are the free availability of qualified consulting specialists in other branches of medicine, of laboratory and visiting nurse services, of family health education, and last and perhaps most important, the fact that 90% of all HIP deliveries are performed by qualified obstetricians.

In the age groups over a year, the utilization rates for the younger children are consistently higher for boys than for girls. There is a fairly high rate for children 1 to 2 years of age, a lower but fairly constant one for those 2 to 4 and 5 to 9, with sharp declines for both boys and girls in the next 5 year period of adolescence. Beyond that the boys show a still lower rate while the girls level off at an even lower rate. After adolescence

the rate for young men begins to rise but that for young women mounts very much more rapidly as they enter the childbearing period. Whatever the pediatric policy of the various medical groups, the utilization rate is always high for babies under one year (averaging 13 to 14 services a year), much lower during the second year, a little less for the next 8 years, and very low for those aged 10 to 14 (well below the general average of about 4 services per year for the entire insured population of all ages). The pattern of utilization is about the same throughout all of the boroughs.

These figures record the experience of 1948. We cannot guarantee that they reflect what will be seen to have happened thereafter, but we have reason to believe that there will be no sweeping differences. In 1949 the proportionate number of services by pediatricians increased a little, probably reflecting the results of the adoption toward the end of that year of the requirement of routine pediatric care for all infants. The general utilization rates for the two years 1948 and 1949 are exactly the same, although the enrollee years advanced from 117,059 to 198,386 and the number of medical services exclusive of those of pathologists and radiologists went up from 500,000 to 850,000. During the current year (1951), about 950 physicians in the 30 HIP medical groups are rendering more than a million and a quarter medical services to an insured population of about a quarter of a million people.

Surgery for Children

Since, even under a very strict assignment of children to the care of pediatricians, other specialists continue to have some child patients, we have explored the HIP experience with surgical services to children. These involve general surgeons, otolaryngologists, orthopedic surgeons, ophthalmologists, dermatologists and other specialists as well as the general physicians who have the care of children.

For the period of the last six months of 1949, during which there was a total of 27,925 years of child coverage, 1,528 surgical procedures were performed on 1,399 different children. Table 4 lists these procedures, classified by the conditions which occasioned them and the places at which the services were rendered. A total of 800 operations were performed in hospitals, 716 in the groups' medical centers or in physicians' offices, and 12 in the children's homes.

The 1,528 procedures were distributed among the specialists and general physicians as follows:

Branch of Medicine	No.	Per Cent
Total	1,528	100.0
Otolaryngology	412	27.0
General surgery	325	21.3
General practice	234	15.3
Orthopedic surgery	181	11.8
Obstetrics	118	7.7
Urology	109	7.1
Dermatology	93	6.1
Ophthalmology	33	2.2
Special pediatric surgery	23	1.5

The surgical procedures reported by the general physicians were, in large part, those associated with injuries and accidents.

TABLE 4

SURGERY ON CHILDREN UNDER 15 YEARS OF AGE, CLASSIFIED BY PLACE OF SURGICAL PROCEDURE, HIP, LAST 6 MONTHS OF 1949

Condition for Which Procedure Was Performed	Place of Surgical Procedure			
	Total	Hospital	Office	Home
Total	1,528*	800	716	12
Diseased tonsils and adenoids	379*	334	45	—
Injuries	342	43	293	6
Phimosis and elective circumcisions	237	207	29	1
Abscess, carbuncle, paronychia and other infections	109	8	98	3
Verrucae	104	2	101	1
Tumors and cysts	72	22	49	1
Appendicitis	70	70	—	—
Hernias	49	49	—	—
Orthopedic conditions	43	13	30	—
Diseased finger and toe nails	29	4	25	—
Eye defects	28	18	10	—
Other conditions including congenital defects	66	30	36	—

* Includes 4 postoperative procedures to stop hemorrhage.

TABLE 5

SURGERY ON CHILDREN UNDER 15 YEARS OF AGE, CLASSIFIED BY AGE AND SEX, HIP, LAST 6 MONTHS OF 1949

Condition for Which Procedure Was Performed	Surgical Procedures by Age and Sex						
	Total	Under 5 yr.		5–9 yr.		10–14 yr.	
		Male	Female	Male	Female	Male	Female
Total	1,528*	503	211	318	200	198	98
Diseased tonsils and adenoids	379*	99	87	94	79	13	7
Injuries	342	75	47	98	42	55	25
Phimosis and elective circumcisions	237	226	—	7	—	4	—
Abscess, carbuncle, paronychia and other infections	109	22	28	15	10	26	8
Verrucae	104	6	4	25	17	24	28
Tumors and cysts	72	18	15	13	5	11	10
Appendicitis	70	5	5	20	17	14	9
Hernias	49	15	3	21	3	7	—
Orthopedic conditions	43	16	10	4	2	10	1
Diseased finger and toe nails	29	1	—	6	2	18	2
Eye defects	28	5	2	7	8	3	3
Other conditions including congenital defects	66	15	10	8	15	13	5

* Includes 4 postoperative procedures to stop hemorrhage.

A majority of the operations were for diseased tonsils and adenoids, injuries, and elective circumcisions. Of those performed in hospitals, tonsillectomies, appendectomies and herniorrhaphies were most common. The circumcisions are usually performed before the newborn is discharged from the hospital.

About 39 of the operations were performed to correct congenital defects such as nevi, hemangiomas, club feet and other foot deformities, strabismus and other eye abnormalities, undescended testicles and other congenital defects of the genitalia and urethra, congenital dislocation of both hips, supernumerary lobe of the ear, congenital torticollis, and congenital heart disease.

The age-sex distribution of the children receiving surgery is given in table 5. The boys exceed the girls both in actual numbers and in rates. The surgical procedures occasioned

TABLE 6

RATES OF SURGICAL PROCEDURES PERFORMED IN HOSPITAL, CHILDREN UNDER 15 YEARS OF AGE, BY BOROUGH OF MEDICAL GROUP LOCATION, HIP, LAST HALF OF 1949

Borough of Medical Group	Rates of Surgical Procedures in Hospital*			
	All Children Under 15 yr.	Under 5 yr.	5–9 yr.	10–14 yr.
Total HIP	28.6	44.2	26.6	12.6
Bronx	27.6	35.6	29.0	17.6
Brooklyn	29.0	45.8	25.0	12.8
Manhattan	32.2	53.2	23.8	14.0
Queens	27.4	43.2	28.2	7.0

* Rates are per 1,000 enrollee years for children in the respective age groups.

by injuries were twice as prevalent among boys as girls. Excluding these as well as circumcisions, the rate of surgical operations for the boys is 38.8 per 1,000 enrollee years and for girls 29.0.

To ascertain the degree of uniformity throughout the HIP experience, the rates for hospitalized surgical cases involving children were determined for each borough (table 6). Hospitalized cases were chosen because we know that some of the medical groups are more meticulous than others in designating as a surgical case the small incidents of minor surgery performed in the medical centers and in doctors' offices, such as small lacerations repaired, minute abscesses drained, and small cysts removed. The hospitalized cases, however, are not subject to this variation in interpretation.

With the exception of the very low rate for the older children in Queens, the rates in the several boroughs are fairly comparable. The slightly higher rates in Manhattan probably reflect the greater necessity for hospitalization which arises in the areas with crowded conditions in the homes and streets. The low rates for Queens may be the obverse of that.

In this connection it should be pointed out that the rates here used are not true annual rates. These rates are based on the last six months of the year and because of seasonal variations may not properly reflect a full year's experience. They are, however, suitable for comparison of the experience of boys and girls and of the experience of the insured population throughout the several boroughs.

Morbidity and mortality studies of the infant population and, in fact, of the entire insured population in HIP are the subject of a special research project which is being financed by several philanthropic foundations. Much of the required information concerning the valuable clinical and demographic experience of the HIP population can be derived from the punch card coding records.

Relation of Prepaid Medical Care to Existing Public and Voluntary Programs

Public and voluntary resources for the health and medical care of children have grown over the years and are now found in great variety and quantity in most American cities. There are many resources for health education, particularly in the field of child health. Health services are offered by public health departments, public schools, and voluntary agencies. Among these are well-baby clinics, medical inspections, diagnostic services for hearing, vision, pulmonary conditions, orthopedic defects, and so forth. Immunizations may be secured from the public health department. Medical care for those who cannot have a private doctor is provided from a wide variety of sources: clinics and the wards of public and voluntary hospitals, emergency care at home for children on public assistance, special medical charities for children with specified diseases such as poliomyelitis, heart disease, tuberculosis. In New York City there are pages of listings of such resources in the directory of social agencies, each set up for a limited type of service to the child and his family.

In the absence of a better system, these are all good. But one comes to ask himself whether that array of limited and piecemeal services does not leave a great deal to be desired as a way of meeting the total needs of children and whether we must not now press for means by which it can be made sure that each child has comprehensive, rounded, and complete health supervision and medical care. We take it that there would be general agreement that it is in the interest both of the child and his family and of the community to cut down the number of different organizations dealing with a given child throughout his childhood, provided, of course, that those responsible for his care are fully prepared to meet his needs in a competent way.

The health education and preventive service program of HIP is of special public health value to children. The effectiveness of an educational campaign is greatly heightened when the advice emanates directly from one's personal physician and when the acceptance of the advice "to see your doctor" entails no financial burden. Twenty-nine of the 30 HIP medical groups issue popular health education bulletins to their respective clienteles at regular intervals. The health education materials are prepared by the central HIP organization, which also carries a major share of the expense of publication and distribution to the subscribers. The central organization also provides the medical groups with the assistance in the field of an adequate health education staff under the full-time direction of a physician expert in preventive procedures and health educational services.

Relation of Family Physician and Pediatrician

There is need for some attention to the problem of restoring the family doctor in this day and age to his rightful place in society and to the need for realigning the converging paths of the general physician and the pediatrician toward the goal of family counselor. When a family enters HIP, it chooses a medical group and then selects one member of the staff of that group as its family physician. HIP contemplates the provision of a doctor who

sees the family as a whole and sees it in its social and economic setting and in its psychological as well as its physiological aspects.

When the wife becomes pregnant, she comes under the care of a qualified obstetrician of the group. Usually before she and the baby have left the hospital, the pediatrician examines the child. After they have returned home, for some weeks all three physicians may be active in the care of the family, the obstetrician for postpartum care, the pediatrician with the new baby, and the family physician for anything else that may arise. When the three physicians are working in close cooperation and the case is an uncomplicated one, this multiplicity of physicians will probably present no problems, since they are all members of a medical team. But it can become tangled and confusing if there is a failure of liaison between them, or if they are not in harmony in general outlook on matters of family health guidance, or if the problems are such as to give rise to honest differences of opinion. To make sure that there will be no such failure means the development of closely knit teams of physicians with active communication between them and with unit record systems which move in the direction of the family type. We believe that our self-constituted autonomous groups of physicians have a very good basis for developing effective working relations and for setting up workable divisions of responsibility.

Under group practice patients become habituated to this situation of having a medical team rather than one doctor. A good working relationship between the general physicians of the families and the pediatricians who carry children up to puberty has been developed without much difficulty by the several HIP groups which follow this policy. Parents learn, as a matter of course, to call the pediatrician for the children under 13, the general physician for themselves and the older children. If, as we hope, the general physicians in HIP come to see patients in their social and economic environment and become true family counselors, the pediatricians may find a sufficient field of operation if they concentrate on the routine care of children at the age when crucial problems of child health are present, before habit patterns are fixed and emotional growth largely determined, that is, in the child's first 4 or 5 years, with consultant responsibility thereafter. That will depend largely upon the quality of care that general physicians are able to bring to bear on the family's problems of mental and physical health. Until there is assurance that they have the requisite preparation for dealing with the health problems of school age children, the pediatrician remains the best resource for these patients.

Mental Health Services in a Program of Prepaid Medical Care

Every HIP medical group is required to have a psychiatrist on its staff for consultation and guidance. It is impossible for such a prepaid health plan to supply a complete child guidance service for children who manifest pronounced psychopathological conditions. There are not enough competent child psychiatrists and their services for children and their parents are too costly to be included in an insurance program. But some preventive services in the field of mental health are within such bounds, especially for young children.

It is in early childhood that the relation of mental health to physical well-being is most intimate and the possibilities of mental hygiene are greatest. A good pediatric service must of necessity concern itself with mental factors in the child's growth and development as well as with his parents and siblings.

The incorporation of psychiatry, preventive and remedial, for children in a prepaid plan would require the services of psychiatrists for more than the diagnosis and advice

which are now available under HIP. Aside from the shortage of well-trained psychiatrists,* a great deal of psychiatry is still in the hypothetical stage—inspired and valuable, but few of its concrete procedures are as yet in the incontrovertible and universally accepted, medically authentic category, if one may rely upon the views expressed by the eminent physicians responsible for the report on *Pediatrics and the Emotional Needs of the Child.*[4]

In pediatrics the measure of agreement on the psychic components of disease may be greater than would be found among general physicians or among some of the other specialties. But such agreement has not yet reached a stage at which there are "accepted practices." In spite of these difficulties, there is a sense of urgency about moving forward as swiftly as possible toward a goal which includes pediatric care that encompasses mental hygiene concepts and specialist services for children who exhibit behavior problems. How that can be done, we do not as yet know but we do recognize the necessity for study, planning and experimentation. Such an experiment is now in progress in one of the medical groups. HIP plans to go forward in this direction just as soon as it can see a reasonably clear road ahead. Until then the field belongs to the pediatricians, within the limits of their capacity to serve.

Summary

1. Under a comprehensive system of prepaid medical care (HIP), the services of qualified pediatricians, as well as of laboratories, clinical specialists, and visiting nurses have been made available to children without any extra charges to prevent their full utilization.

2. The 63,500 children under 15 years of age enrolled in HIP on March 1, 1951, constituted 24.5% of the total insured population on that date (259,170). Of these 36.0% were under 5 years, 34.6% between 5 and 9 years and 29.4% were aged 10 to 14.

3. Of the 5,500 children born into HIP since it was established four years ago, 90% were delivered by qualified obstetricians.

4. Since 1949 all infants are routinely under the care of a qualified pediatrician at least until the end of the first year of life, 48.5% of HIP children are cared for by pediatricians to school age, and almost 32% receive all their routine care from pediatricians to the age of puberty.

5. Of the 62 qualified pediatricians on the staffs of the 30 HIP medical groups, 40 are diplomates of the American Board of Pediatrics.

6. HIP has one pediatrician for each 1,025 enrolled children under 15. This is 2½ times the proportionate number available to children living in the larger urban centers of New York State, assuming that all of the pediatricians in the State are located in such areas.

7. In medical groups in which pediatricians provide child care to puberty, the proportion of home visiting is high as compared with their medical center, office, and hospital services; 34% of their services are home calls, 59% medical center or office calls, and 7% are rendered in the hospital. The pediatricians who serve chiefly as consultants do much less home visiting (8.4% of their total services) but provide a much higher percentage of medical center and office services (79.3%) and also a higher proportion (12.3%) of their services in the hospital.

* The American Academy of Pediatrics report states that there are only 2,000 psychiatrists in the United States and of these only 42% were certified as of 1947-1948.

8. Children under one year average 13.1 physicians' services per year, many of a purely preventive nature. Age-specific utilization rates have been computed for the 1948 experience on 500,000 physician services and are reported in this paper.

9. HIP's neonatal mortality rate was about 9 per 1,000 live births, whereas the rate of New York City as a whole during the same year was 20 per 1,000, of New York State 20.7 per 1,000, and of the country about 25 per 1,000.

10. An analysis is reported in this paper of HIP's experience with pediatric surgery during the last six months of 1949, which included 1,528 surgical procedures in relation to 27,925 enrollee years of children.

11. Although consultant services of psychiatrists can be provided under a comprehensive system of prepaid group practice, the pediatricians of the medical group must continue to carry the responsibility, as in any other system of medical care, for that large part of medical practice which is concerned with the behavior and emotional problems of childhood. In comprehensive group practice it has therefore been found desirable for the pediatrician to relieve the family physician of the routine care of young children in the family, at least during infancy and the preschool period.

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TRENDS

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This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

UNICEF CONTINUES UNDER REDUCED APPROPRIATIONS

SINCE it was established in 1946, the United Nations International Children's Emergency Fund has been a powerful influence in marshalling both funds and personnel in the interests of children throughout the troubled and underdeveloped areas of the world. For the needs of UNICEF an appropriation of $5,750,000 has been approved by the Senate and the House for the current fiscal year (July 1, 1951-June 30, 1952). This appropriation, which now awaits the approval of the President, is a marked decrease from the $15,000,000 authorized last year, or even the $12,500,000 requested by the President for this year. Furthermore, a report which still stands on the record as far as the House is concerned, stipulates that the U.S. contribution should not exceed 33% of the amount contributed by other governments, a marked change in the matching formula in which, heretofore, the United States has contributed 72% with 28% from other countries.

The funds contributed by the United States, limited as they are for a world program, have stimulated other countries to meet the matching requirement and thus make larger contributions of their own. Forty-eight countries have contributed to the fund. Also, it may be noted that the bill as passed refers to the total amount contributed by other governments; the Senate in its report indicated that the total amount might include internal matching by other governments as well as the regular contributions of donor countries. If such an interpretation can be agreed upon, then the full amount of $5,750,000 will call for approximately $9,000,000 of matching funds.

In the past year there has been considerable discussion about continuation of the fund. It was originally established as an emergency postwar measure to rescue large masses of destitute children from starvation and death. The question now arises whether we are still dealing with an emergency or with continuing and ever present problems. Should other UN agencies include the special needs of children in their long range technical assistance programs? How should the funds be spent? Should large funds continue to be expended upon the distribution of supplies: food, shoes and medical supplies? Or should emphasis shift in the expenditure of the limited funds to technical assistance, demonstrations and aid in the construction of plants for production of essential medical supplies such as penicillin and DDT?

These and related questions have been given serious consideration in recent meetings of the U. S. Committee for the UNICEF. At a meeting held June 7, 1951, in New York City, Miss Katharine Lenroot, U. S. Representative to UNICEF, outlined some of the policies and principles to which the fund will try to adhere in the coming year. She stated that:

1. The fund will concentrate on meeting the emergency and long range needs of chil-

dren, particularly in underdeveloped areas, through the provision of supplies, training and advice. The fund will concentrate mainly on maternal and child welfare and child feeding programs, taking into consideration the work of the specialized agencies of the technical assistance and fellowship programs.

2. Priority will be given to projects which have the greatest impact on large numbers of children, which assure long range benefits and which deal with basic needs in child care.

3. Emphasis will be placed upon meeting the needs of children by increasing local production facilities so as to insure continued supplies in the future. A case in point is the contribution of $850,000 in equipment and supplies as UNICEF's share of the project to help India construct a penicillin production plant costing several million dollars, the first penicillin plant in all of South Asia. Similarly, following the closing of Asia's only DDT factory in Formosa, UNICEF allocated $200,000 to Pakistan and $107,000 to Ceylon for such plants. UNICEF has also aided in production of BCG at a growing plant near Manila. Additional equipment for BCG laboratories is on its way to Pakistan, Ceylon and Malaya. Indonesia, Thailand and Burma hope to open BCG laboratories with UNICEF aid.

With this shift in emphasis, it seems likely that UNICEF may become less of an emergency measure and may be established on a more permanent basis as an agency to help underprivileged nations help themselves in developing the services and facilities essential to the health of their children.

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

CHILD HEALTH IN GUAM AND THE PHILIPPINES

MEDICAL supervision of the health of well children has been a fundamental method for prevention of disease and promotion of child health. The Academy's study showed clearly how considerable a role such supervision played in the total field of child care. In parts of the world which are much less developed technically than the U.S.A., the problem of child health supervision may have a different focus. Separation of ill and well children may not be easy; growth standards may not be easy to establish. Two recent pieces of information relative to child health in the Western Pacific area describe the kinds of problems mentioned.

At a meeting of the Philippine Pediatric Society, March 28, 1951, Dr. Carlos Ferrufino* reported on the findings in well child conferences now being conducted in the rural area of Quezon City. These activities are a part of the Rural Health Demonstration and Training Center Programme which is a joint undertaking of the Philippine Government, United Nations Children's Endowment Fund and World Health Organization. The Novaliches-Talipapa zone has a population of 8,183; operating in the zone are one main health center which is located 18 km. outside of Manila, and a sub-center in Talipapa located 14 km. outside of Manila.

Shortly after the arrival of the World Health Organization consultants, and in accordance with previous plans, well child conferences were established as a specialized activity in the above mentioned health centers. Despite the implied limitations of the name it is impossible to deal only with healthy children if the community has no other medical facilities outside of the health center. It was therefore agreed by the staff to receive at first all children under the age of 6 years regardless of condition, and to screen them gradually by referring the sick ones to the general clinics of the same health center, as well as by intensifying the home visits.

The study covered the first 216 children who attended the health centers from the inauguration of the well child conferences on October 18, 1950 to January 17, 1951. This group represents 11.3% of the 1,910 children under 6 years, who live in the area. Thirty-seven per cent of the examined group were found healthy while the remaining 63% were considered unhealthy.

Evaluation of the height and weight measurements which were made is obviously difficult, in the absence of serial studies and in the absence of reliable height-weight tables for Filipino children. For rough comparative purposes, however, table 1 shows the distribution of 80 apparently healthy Filipino children in the percentiles established in the growth studies at the Harvard School of Public Health.

The pattern is not greatly distorted under 6 months of age but thereafter the Filipino children appear to concentrate more in the lower percentiles. Whether the explanation is nutritional or due to other factors is not apparent from the data.

* Grateful acknowledgment is made to Dr. Ferrufino for supplying the tables and comment for use in this column.

The diagnoses among the children considered unhealthy are listed in table 2. It is rather surprising that only 144 diagnoses are listed for the 136 children. More commonly these children are suffering from multiple diseases and it may well be that the list should be even longer. Malnutrition heads the list. This diagnosis represents a combination of clinical signs, not just a single one. The minimum signs required were (a) loss of subcutaneous tissue, (b) pale, wrinkled skin with poor turgor, (c) marked bony eminences, (d) sunken abdomen, (e) flabby muscles, (f) low weight and height, (g)

TABLE 1

DISTRIBUTION OF 82 APPARENTLY HEALTHY FILIPINO CHILDREN IN HEIGHT-WEIGHT PERCENTILES OF HARVARD SCHOOL OF PUBLIC HEALTH

Age	Total Children	Harvard Percentiles						
		3	10	25	50	75	90	97
0– 6 mo.	37	7	2	7	9	6	3	3
7–12 mo.	13	6	2	3	2			
13–24 mo.	16	9	2	3	2			
2– 6 yr.	16	14	1		1			

TABLE 2

DIAGNOSES AMONG 136 UNHEALTHY CHILDREN

Malnutrition	37
Skin Diseases	29
Advanced Dental Caries	20
Respiratory Diseases	19
Helminthiasis	9
Gastroenteritis	6
Prematurity	4
Hernia	3
Malaria	2
Otitis Media	2
Tuberculosis	1
Miscellaneous	12

intercurrent infections, especially of the gastrointestinal tract, skin, scalp, (h) advanced caries and (i) history of inadequate food intake.

It was surprising that not a single case of infantile beriberi was seen although this illness is considered one of the greatest killers in the Philippines. Further investigation indicated that the apparent contradiction lay in the great inaccuracy of the diagnosis of infantile beriberi. It is very rare in children's hospitals but commonly given as a cause of death for children dying without medical care. By contrast, very rarely is the cause of death listed as unknown. In all probability "infantile beriberi" is being used as a "waste basket diagnosis" without any real evidence of its existence.

Of the skin diseases, impetigo is the chief problem. It should be noted that intertrigo and minor skin lesions were not considered in this item.

The diagnosis of helminthiasis or malaria was made only upon laboratory confirmation.

Dr. Ferrufino concludes that further study of the causes of malnutrition is essential, that economic conditions are of fundamental importance, but that education in the proper use of foods which are available would go a long way toward correcting some of the more obvious difficulties.

A report by Greulich (Am. J. Phys. Anthropol. 9:55-70, March, 1951) presents a careful analysis of height and weight measurements in children on Guam, carried out in 1947.

The study included 1,800 children, 1,726 between 6 and 17 years of age; 880 were boys and 846, girls. They represented about 19% of the Guamanian children of school age. Children were examined from a number of villages to obtain a representative sample.

For comparison children studied at the Brush Foundation Study of Growth and

TABLE 3

AVERAGE STANDING HEIGHT (CM.)

Ages	Boys		Girls	
	Guam 1947	U.S.A. (Brush Foundation Study)	Guam 1947	U.S.A. (Brush Foundation Study)
6	107.1	117.7	106.5	117.6
7	111.8	123.8	111.5	123.8
8	116.9	129.9	116.5	129.8
9	120.4	135.4	120.9	135.3
10	125.1	141.0	126.4	141.0
11	130.1	145.9	132.0	147.7
12	133.4	151.4	136.6	154.2
13	139.2	157.5	143.3	159.5
14	143.5	164.8	147.7	162.9
15	149.4	171.1	150.9	164.8
16	155.1	175.2	151.5	165.5
17	159.3	176.6	150.9	165.4

Development (recently completed at Western Reserve University, Cleveland) were used and table 3 presents some of these data.

"The absolute differences in average stature between the Guamanian and the Cleveland children throughout the age period studied are probably chiefly racial in origin, but they are due in part, also, to differences in the nutritional and health status of the two groups. The children in the Brush Foundation Study were carefully selected from families who were well above the average economic level of the Cleveland population. Their superior nutritional and health status is attested by the fact that, throughout the period from infancy to adolescence, their average height and weight were significantly greater than those of the average child population of the United States.

"Despite marked differences in average stature between the Guamanian and the Cleveland children, there is a close resemblance in the shape of the growth curves of those of the same sex in the two groups, the growth curves of the girls being especially similar. There are some differences, however, in the age at which certain changes in the shape of the growth curves occur."

Both boys and girls on Guam experience their prepuberal spurt later than those in the

Brush study. The period when boys have lower stature than girls of the same age is also longer in Guam, being about 6 years, as compared with the average of 3 years in Cleveland.

Skeletal age was measured by roentgenographic study of the wrists. Here, too, significant retardation was apparent in both boys and girls in Guam as compared with the Brush Study. Other studies, including the height-weight index and measurement of sitting height, gave similar pictures.

The author believes that the observed relative physical retardation on Guam is due only in part to racial differences and that some, perhaps much, is due to food deprivation and other hardships. The Guamanian boys were found to be relatively more retarded than the girls in growth and in skeletal status. This is consistent with the view that the human male is less successful than the female in withstanding the rigors of an unfavorable environment.

Both of these studies, from populations less favored economically than the U.S.A., present problems in child health which have implicit lessons for pediatricians in America. Basic growth patterns are the same everywhere, but distortions may easily be related to inadequate food and poor general sanitary status. Standards of environmental conditions, nutrition and health supervision, accepted as ordinary in a wealthy country, ought not be taken for granted. Continued effort is necessary to maintain and improve the health status of our children.

SPECIAL ARTICLE

PEDIATRIC POTPOURRI

By ALFRED H. WASHBURN, M.D.
Denver

EVER since accepting the kind invitation of your President I have known what I wanted to talk to you about tonight. However, when it came to giving my talk a title—a label which would suggest my main theme—then I was stumped. I want to talk a bit about a number of things—about the Child Research Council, about human growth, about education, about pediatric research, and about the responsibilities of the pediatrician in the half century ahead of us. I might then call the talk a "Pediatric Potpourri." The only difficulty with this title is that Mr. Webster, in his fourth definition of the term, says, "a literary production composed of parts brought together without order or bond of connection." While it may be that some of you will decide by the end of this talk that it has been a veritable potpourri yet I hope to succeed in welding a definite "bond of connection" between the various topics discussed. Perhaps the growth, the development, and the adaptation of the human organism is the cementing substance which should run as a golden thread of continuity from the beginning to the end of my discourse.

I have used the term "human development" rather than "child development" because my talk tonight is as much concerned with the development of mature and thoughtful pediatricians as it is with the sound and happy development of children who may some day become physicians, lawyers, engineers, businessmen or senators. In fact I'm going to start talking about the Child Research Council not merely as a particular sort of research approach to child development but also as an educational experience for the investigators involved in the venture. It is well to remember that for each of us our own most valuable tool in research is not a Beckman spectrophotometer, a Tiselius electrophoresis set-up, or any other such apparatus, but one's own Self. If this truth is accepted then it becomes obvious that the growth, development and adjustments of that Self in its environment become of supreme importance. Thus it hardly seems necessary to apologize for the fact that, in talking about the Child Research Council, I shall be involved also in a sort of autobiographical account of the development of my own thinking.

In 1930 I moved from a busy pediatric service at the University of California to the job of reorganizing and administering a child research program in Denver. In the early thirties our orientation was pretty much that of medicine and the medical sciences. We had decided, at the start, to follow individual children growing up. There was, of course, a vast body of knowledge and wisdom from the biological sciences which suggested clearly that a sound approach to the problem of gaining a more adequate understanding of any living organism was to follow the whole growth and development of individual specimens of the organism in question. It was many years ago that Frank Lillie remarked that any biologic unit is its own life history from gametes on. But many difficulties beset

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us. Our own Board of Control wanted immediate results applicable to the welfare of the children in our community. Physicians of the community were either skeptical or frankly hostile in many cases when the subjects we accepted for study were their own patients. In the absence of any offer of therapeutic service the lay people were none too enthusiastic about participating. And worst of all, our own concepts of how to set up and conduct such a research program were far from clear.

There is great comfort and a sense of security in setting up a neat experiment in the laboratory where variable factors can be more or less controlled. I still indulge in them myself. From previous experience one proposes an hypothesis as, for example, that there is a straight line relationship between the concentration of fibrinogen and the rate of sedimentation of erythrocytes. Then one controls all the other factors influencing sedimentation such as size and position of the tube, temperature, and concentration of red cells and of other proteins. Fibrinogen is added in graded amounts to successive tubes and eventually a curve is constructed from the resulting sedimentation rates. It is found to form a straight line on the chart—the more fibrinogen, the faster the rate. The simple hypothesis has been validated. One might then develop a theory concerning the mechanism by which the fibrinogen increased the sedimentation, proceeding to set up further experiments. I am not for a moment belittling the need for nor the usefulness of such experiments! All our staff from the psychologists to the research technicians in x-ray and photography become involved in just such experiments. Rather I want to point out that we were faced with the fact that so simple a concept of research was hardly adequate for the extraordinarily complex problems encountered in studying human biology.

It was inevitable that in the early years we had to do a lot of exploring and feeling our way. We were often accused—occasionally quite justly—of being just another data-gathering institute. It took time, many observations, much data gathering and analyzing, much studying, thinking, and discussion before we were in a position to formulate hypotheses and orient our observations and investigations in such a way as to offer hope of validation or invalidation of theories of human development. It should not be a source of surprise to any thoughtful pediatrician that we now suffer from a plethora of such theories—the real problem being how they may be proven or disproven.

Unfortunately one cannot do much exact experimenting on human beings. Fortunately, if one has time and patience, "Nature" sets up many beautiful experiments. These may be accurately observed. The factors which influenced the course of events or changes may be sorted out, the necessary causes without which the changes would not have occurred and the added so-called sufficient causes which made the observed changes inevitable. On the basis of one's own and others' observations one evolves theories concerning sufficient and necessary factors in the development of certain traits or characteristics, be they physical, physiological, psychological or social. One then observes or actually elicits the evidence in infancy or early childhood of the presence or absence and relative strength of these hypothesized factors. On the basis of this evidence one makes predictions. For example, in the absence of the necessary causes to produce certain traits this individual will not ever show such traits as he grows through childhood into the mature years. We are interested in traits as varied as hypertension and schizophrenia, susceptibility to infections or environmental stresses, efficient utilization of food, or aggressiveness of social behavior. By carefully oriented observations and tests through the life span we discover whether our predictions based on our hypotheses are correct or not. We have attempted to set up an institute to carry out this sort of research program on a permanent basis so as to follow

through a series of human generations. I should like to describe briefly certain aspects of the program.

We are following a small group of subjects in a very intensive manner. They are a fairly homogeneous group as far as any Americans are, being mostly representatives of Denver's stable middle class and mostly of North European ancestry. Thirty-five of our 175 subjects are now over 20 years old. The remainder are fairly evenly divided by 5 year age groupings from 0 to 20, with 3, as yet unborn. During the past 5 years most of the new infants including 4 second generation babies have been enrolled in the study series between 5 and 8 months before birth. These children and their families represent our human material.

We do not, however, think of these people as guinea pigs, to be used as a means for us to make contributions to some specific field of science. We have a research staff of 29 people who think of the sciences—medical, biological or social—as tools with which to gain a better understanding of the dynamics by means of which each of these subjects is developing into an individual person with his or her own unique characteristics. Five of the staff are primarily concerned with the investigation of structural changes—of the varying patterns by which each individual reaches his final physique. Six of the staff are chiefly concerned with the psychological and social factors involved in personality development. Seven of the investigators are mostly occupied with nutrition, metabolism or chemical changes during growth. The remainder are involved in the pediatric evaluation of health and disease, in a combination of studies including both physical growth and physiological development, or other miscellaneous duties. We try to remember that the individual child being followed is, after all, as the term implies indivisible—that he is a biologic unit—that only for purposes of analysis are we justified in considering physique, physiological or biochemical functioning, and personality characteristics or temperament as separate entities. Such a philosophy necessitates close team work between staff members in different disciplines.

The inter-relatedness of the various investigations can be demonstrated by taking almost any one field. To illustrate this I might take the study of nutrition. The nutritionist obtains a rather complete record of food intake, starting with monthly home visits prenatally for a picture of the mother's diet and continuing with the baby from birth on. These records undoubtedly hold much of interest for nutritionists and dietitians but for us such a contribution to dietetics is merely a useful biproduct of our main program of research. We are primarily interested in how Jimmy or Molly differs from the average or group pattern, why his pattern of eating is different, and what significance it has for his future growth and ultimate health and happiness. And so we turn from his record of food intake to an examination of his blood vitamin levels, his blood cell levels, his plasma protein levels and his basal metabolic rate. Then we wonder about his health record—and perhaps turn back again to see what his gamma globulin level did after that recent attack of measles. Over a longer time period of continued deviation in his dietary pattern we become interested in seeing if there is any effect noticeable in the pattern of his bone growth or epiphyseal development. The dentist and nutritionist compare notes. We examine with care any deviation from his expected pattern in growth rate as shown by the measurements taken on either x-rays or photographs. At the same time we check on the extensive data concerning psychological and social factors in Jimmy and his family. This is, of course, a two way process. For example, there are times when the nutritionist brings in from her home visits valuable data for the psychologists and times when the psychologist, psychiatrist or

social worker furnish the clues for explaining an unusual eating pattern. Finally, Jimmy's performance on the battery of functional tests comes under scrutiny—perhaps his reaction time is slow or his efficiency on the bicycle ergometer not up to scratch.

By studying these relationships, by becoming aware of the truth that patterns of development in one area are related to things going on in all other areas of the individual, one becomes more adequate in diagnosing the fundamental source of trouble and knowing what should be done about it. In fact, without such understanding the pediatrician is very apt to miss the essential handicap which is interfering with the orderly progress of healthy growth, contenting himself with treating a symptom. Unfortunately our present knowledge of these inter-relationships is still woefully inadequate. We have, I believe, only barely scratched the surface in gaining an understanding of those clues which we should be able to pick up early in life, and which should tell us of trouble in the offing if nothing is done to correct the situation. This would represent "preventive medicine," or positive health preservation, at its best. I shall return to this thought in a few minutes but first want to mention two experiences which lead me to believe that already we have made enough progress to be useful in leavening the education of medical students, interns, and residents.

I am asked quite frequently what sort of a course is needed in "growth and development" as though this were some sort of specialty, like ear, nose and throat, which should be represented in the curriculum by so many hours. Young pediatricians, about to take their Board examinations, sometimes come in to ask me what they must know about "growth and development" to pass their examinations. Even members of the Board have wanted a handbook containing the essential "facts" which the young pediatrician should know. It seems to me that all these reactions represent a misconception about the nature of growth. Surely we want every doctor and most especially every pediatrician to be able to understand his patient as a person rather than just as a case of pneumonia or rheumatic heart disease. As that wise old clinician, Sir James McKenzie, pointed out many years ago, no two patients with the same disease present just the same picture. Furthermore we all recognize today the necessity for treating the person rather than the disease. But how can the pediatrician properly evaluate the person who is his patient without considering how he "got that way." A child of 5 years is as he is and does as he does because of everything that has happened in the interplay between his gene-determined characteristics and his environment since conception. He can be understood only in terms of his growth, development and adaptation. To be sure we never have any chance of knowing it all. But the more we know about what is likely to happen—about the common human patterns and reactions during growth, together with the most likely deviations and their common causes—the more adequate we shall be in history taking, in examination, and in our interpretations of our findings. Growth and adaptation are, then, part and parcel of pediatrics —the very warp and woof of the material with which every pediatrician must deal whenever he has a child entrusted to his care. This brings me to the first of the two experiences I wanted to mention, namely, with medical students.

With a strong feeling that an understanding of the growth, the maturation, and the adaptations of the human organism should be the continuous theme which integrates the basic sciences and the clinical subjects alike, we started a series of exercises for the freshman class at the University of Colorado School of Medicine. These exercises run through the first half of the first year starting on the opening day of school. They consist in lec-

tures, demonstrations, seminars and informal discussion groups. The purpose, which is to introduce the students to the concept of medicine as human biology, involves a consideration of how the medical and related sciences contribute to our understanding of the growth, development and adaptation of any given person who will, one day, be the student's patient. Physical growth, personality development and the course of physiological and biochemical functions from the fetus to old age are discussed with special emphasis, of course, on the period from birth to maturity. Examples of distortions due to disease are demonstrated and discussed by several faculty members representing different departments.

This is admittedly an educational experiment. The four years during which it has been in progress represent too short a time for any but very tentative conclusions. However, I think there is already evidence that the junior and senior students have a somewhat different attitude than formerly. They seem definitely more aware of the need to understand their patients as people with many factors and problems which affect the significance of the symptoms they present. Their questions show at least improvement in their understanding of the interplay between psychological and social factors which are involved as well as in the part played by previous life experiences. If our own knowledge were more adequate we could be of greater service to them. I believe the better students are receiving good stimulus to go on studying and learning from their own experiences. And I'm sure these exercises have given many of the students better insight into their own selves as the instrument they must use in observing and interpreting the patient's deviations. And finally I believe that the 15 participating members of the faculty, coming from eight different departments of the school, have also learned and been stimulated to further learning.

The second experience I want to mention is with pediatric residents. For several years now we have been taking residents from the Pediatric Service for a three months' stay in the Child Research Council. They become temporary members of the staff, taking their turn examining children, having conferences with the various investigators, and tackling some one small bit of search for new knowledge themselves. Two results have impressed me greatly. The first is the striking change which has taken place in nearly all of them in their writing up of their examinations of the children. Items which apparently they never considered worth noting begin to appear. They tell me that they are actually seeing things they never saw before in doing an examination. Usually in going over the first few descriptions of babies which a resident writes I am sure I would not be able to recognize the baby if I saw it—nor could I, on the basis of their descriptions, distinguish between two different babies of approximately the same age and size. But after they have been with us for a month or two I would have no such difficulty in spotting which baby they were describing. We have been at this long enough now so that I can say with some confidence that the majority of these residents are convinced that this increased understanding they picked up during those three months is of great value to them in practice. A recent letter —not written to me—from one of these boys stated that the insights he caught from his experience with us were more useful to him in handling the daily routine run of patients than any two years of hospital ward experience. Perhaps he was exaggerating for it was written to another resident who was debating whether he should take three months with us. But I believe there is good evidence that this sort of understanding is making better pediatricians of these young men and women.

Having just used the phrase "better pediatricians," perhaps I might attempt to say

something about the responsibilities which would appear to be facing the conscientious pediatrician in the years ahead—the years of practice for which we are now preparing students. Ever since the days of Jacobi pediatricians have been leaders in the field of so-called "Preventive Medicine." In fact, they were amongst the first physicians to show a realization of the fact that a good program consisted in something more than the mere prevention of specific diseases by vaccination and immunizations. Their work in well baby clinics and school health programs for over half a century has shown that they had really envisaged the challenge of safeguarding health before disease or disaster had threatened.

Similar leadership was shown by pediatricians, in the decades between the two world wars, in establishing sound research programs which sought to apply and extend the knowledge from the rapidly expanding fields of biochemistry and bacteriology to the recognition, understanding and control of disease and disorder in infants and children. Tremendous strides were made in the treatment and control of serious diseases of infants and children with a gratifying lowering of morbidity and mortality rates. During recent years, however, the increasing potency of the antibiotics in controlling serious infections has not been an unmixed blessing. Many a physician—conscientious enough but with a heavy practice load—has found it far too easy to give maximum doses of penicillin, streptomycin, etc., without even bothering to establish a diagnosis other than that the child was obviously ill with a high temperature. There is apparently little or no thought given to the long time effect on the child, either immunologically or psychologically speaking. That is, the very efficiency of some of the modern forms of therapy are making the busy physician even less curious than before about the factors which may influence the growth and development of the child, and which may determine the kind of adult he is to become.

It seems to me time we paused in our sometimes frantic course which we hopefully call "progress" and ask ourselves honestly where we are going. Our heritage is one of idealism. I am inclined to think the pediatricians today are still the most idealistic group in the medical profession. Hadn't we better examine our goals again and see if our course doesn't need reorienting? I assume that we believe we have the responsibility for helping parents to safeguard the health of their children in such a way that they may reach adult life as healthy and as happily adjusted mature citizens of whom the parents can be proud. The babies whom we look after today will soon be the adult citizens of our Democracy. Even with our present very imperfect understanding of growth and adaptation we have really incontrovertible evidence that many influences which play their part in the early years of life have a profound effect on the later behavior, happiness and even physical health of the individual. In view of these considerations it is difficult indeed to escape the conclusion that the pediatrician has the moral obligation to familiarize himself with these factors as well as he has familiarized himself with the doses of the antibiotics or the amount of ACTH to give a rheumatic fever patient. In terms of the final crippling of the life of his patient, or making him a liability rather than an asset to our democratic society, it might even be more important to be able to recognize the dangers in a distorted mother-child relationship in infancy and know what to do about it.

I don't want to be misunderstood at this point. I am not asking that each pediatrician be his own psychiatrist—although he certainly should be aware of the possible need of a parent for psychiatric care just as he wouldn't hesitate to refer the parent of one of his patients to a surgeon when there were signs of an acute appendicitis. But the baby's prob-

lem is not a psychiatric problem at this stage—rather it is a problem of normal personality development which is an inseparable part of the whole growth picture.

We have a youngster in our study series whose mother, under the guise of being an unusually conscientious mother has carried on a hostile, punitive campaign which is warping the growth and endangering the health of the boy. He has been treated so vigorously for some of his minor ailments that he has been more miserable from the treatment than from the disease. He has had three completely unnecessary operations. The pediatrician has served as an unconscious accomplice in carrying out the mother's punitive measures because he is completely unaware of the symptoms and signs of trouble in this area. The whole problem of constipation in the preschool years—a condition for which the average physician prescribes laxatives, enemas, suppositories or a change in the diet—can hardly be handled sanely without an understanding of the nature of that stage of the development of human beings and the relationship between mother and child during the "bowel training" period. All problems have some psychological aspects or implications but obviously there are many which originate in the physico-chemical area. We have had children put to bed by the physician because the sedimentation rate was said to be high when actually it was merely at the top of the range of healthy variation and right at the child's own usual "normal" level. We have known of adolescents hospitalized with a diagnosis of rheumatic fever with enlarging heart because the physician was unaware of the great spurt in heart growth which usually accompanies a larger than average adolescent spurt in height and weight increases.

I could document my argument at much greater length but am sure my point is clear to you. We who are teachers have the responsibility of seeing to it that the pediatricians whom we turn loose on the public do have an awareness of current knowledge in the field of growth—not merely figures for height and weight and head size or for heart rates and blood pressures but for growth of the whole well or poorly integrated biologic unit. We must attempt to help them gain better insight into themselves in order that they may more easily and more sympathetically understand what the infant, the preschool child or the adolescent is going through.

As they gain such insight they will learn to think of growth as a dynamic process—as a continuous series of fascinating activities in which there is interplay between many factors contained within the organism as well as between those in the organism and in the outside environment. They will learn to think in terms of the biological physics and chemistry of the cells, which leads to cell multiplication, which is the basis of all biological growth—of the electrolyte balances, the action of enzymes and hormones and the functioning of organs and organ systems, so necessary to growth changes—of the changes in the size, contour, proportions and functioning of the organism as a complex but unified whole—and finally of the reactions and interactions between this whole person and all the other individual people who together constitute the larger social unit, whether it be family, state or nation. If they can learn to think in these terms then height or weight becomes more than a mere number—it becomes a point on a continuous curve whose pattern of change leading up to, and going on from that point, is a reflection of this dynamic process. They must, then, become concerned with the "doing" and the "becoming" of the organism more than with its status on some given day. We all know how impossible it is, in many instances, to evaluate the healthiness of the growth process in a youngster except by following him over a time period.

It would be a significant step forward if we could turn out pediatricians with such an awareness of the nature of human growth. But there is one further challenge I should like to throw out. I do not wish to belittle in any way the value of current pediatric research, and certainly I have no desire to decrease its volume or alter its course, yet I believe there is urgent need at the same time for increasing and broadening the investigations into the factors in human growth and adaptation which are responsible for so many of the ills, the unhappiness and the maladjustments of our adult population. It's really difficult to think of anything our present world needs more than a better understanding of how to help parents to rear their children in such a manner that they will turn into adult citizens capable of living together in peace, free of the fears and tensions and bodily ills which make our world today so miserable.

I should like to see the pediatricians living up to their heritage of belief in democratic ideals and of leadership with vision for the future. I have already pictured for you the problem that challenges. It must be tackled with boldness and enthusiasm as well as with patience and long time planning. The interest and wisdom and help of scientists from many fields must be enlisted, for this is a job which requires team work amongst varied personnel, representing all the physical, biological, medical, and social sciences involved in understanding Man. We need to build up a group of institutes, in different parts of the country, each investigating the life cycle of individuals representing a sampling from their own community. Perhaps no two such institutes would be making quite the same approach but all might have enough observations in common to be able to compare notes.

For instance, one might concentrate more of its effort on a particular level of biological organization such as could be approached through vitamin, enzyme, hormone, protein and other chemical studies, while another might spend its maximum effort on changes in growth and adaptation at the psychological level. But each would carry out enough of the basic measurements of physical, physiological and psychological changes so that the knowledge of the two institutes could be pooled and correlated. It would probably necessitate some sort of central or national institute to serve not as a regimenting force but as a center for correlation and stimulation of the efforts in the centers scattered across the country. Such a central institute could also serve as a means for building up adequately trained personnel through a fellowship program—an acute need in the planning years.

I realize full well what a costly program this would be—especially if carried on as it should be through several human generations. However, the financial needs for a given year would be tiny compared with the sums now being spent on armaments. Moreover, we who deal with children should have faith that such a program, once well under way, would do much more for ultimate peace in the world than any amount spent on the means for destruction. I would have great faith that such a carefully planned long time research program, adequately financed, would lead to increasing respect for the dignity and individuality of each citizen—for his need for freedom from regimentation in his growth —for his right to sympathetic understanding of his problems of development and adaptation to his world so that he could contribute his best and realize his finest potentialities as a citizen of the world.

NEWS AND ANNOUNCEMENTS

Dr. Harold E. Mann has joined the staff of the Children's Bureau, Federal Security Agency, as psychiatric services consultant. One of his functions will be to see that all programs undertaken by the Bureau are geared to modern mental hygiene concepts.

In this capacity, he will assist Dr. Katherine Bain, Associate Bureau Chief, in planning Children's Bureau programs so that they will take the emotional needs of children into consideration. He also will work with the Bureau staff, both at home and in the field, on a consultative basis and will represent the Bureau in the field of mental and emotional development of children and youth.

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The Pediatric Staff of the Cook County Hospital announces the third Maurice Lamm Blatt Memorial Fund lecture by Dr. Irvine McQuarrie, Professor and Head of the Department of Pediatrics, University of Minnesota, who will talk on "Clinical and Experimental Studies on Hypoglycemia." This lecture will be given Tuesday, Oct. 2, 1951, at 8:30 P.M. in the Medical Amphitheatre of the Cook County Hospital.

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The following diplomates have been certified by the American Board of Pediatrics, Inc.:

Detroit—June 8, 9 and 10, 1951

Bacon, A. Maynard, Jr., 4619 Marble Hall Rd., Baltimore, Md.
Becker, George H., 210 Lister Bldg., 4500 Olive, St. Louis
Beesley, James Chester, 213 N. Broad, Lancaster, Ohio
Bellin, Leonard Bernard, 325 Angell St., Providence, R.I.
Brodsky, William A., School of Medicine, Univ. of Louisville, Louisville
Bryan, Eunice Elizabeth, 19070 Ballinger Way, Seattle
Bush, Louis G., 804 E. Center St., Pocatello, Ida.
Butler, Hugh H., 165 Shoreham Drive, Rochester, N.Y.
Cale, Ellsworth Ferrell, 33 Ponce de Leon Ave., N.E., Atlanta, Ga.
Cobley, George Gordon, Capt. MC 0-1921805, A.S.U. 117, USAH, Camp Edwards, Mass.
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Coleman, Allan Bertram, 1433 Whittier St., N.W., Washington, D.C.
Cone, Thomas E., Jr., 108 N. Stanworth Drive, Princeton, N.J.
Davis, Marvin L., 2 N. Garfield Ave., Alhambra, Calif.
Eagle, J. Frederick, Jr., 366 Lincoln Parkway, Buffalo, N.Y.
Feeley, Marshall John, 505 Pleasant, St. Joseph, Mich.
Forman, Carolyn Wood, 525 E. 68th St., New York City
Gajdusek, D. Carleton, The Children's Medical Center, Boston
Goebel, Carl William, 213 W. Jefferson St., Ft. Wayne, Ind.
Goodwin, Marvin Harold, 416 N. Bedford Drive, Beverly Hills, Calif.
Green, Morris, Dept. of Ped., Univ. of Ill., College of Med., Chicago
Hellmann, Charles H., Professional Center, Glen Cove Ave., Glen Head, N.Y.
Hodes, Louis, 444 Central Park West, New York City
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Line, Felix G., 710 W. Hill, Knoxville, Tenn.
McCloskey, George Albert, 197 W. Madison St., Rochester, Pa.
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ERRATUM

Symposium on BCG Vaccine, PEDIATRICS, June 1951 issue. In the discussion by Dr. Milton I. Levine on page 862, the second line of the third paragraph should read: "of viable organisms in the first 24 hours . . ."